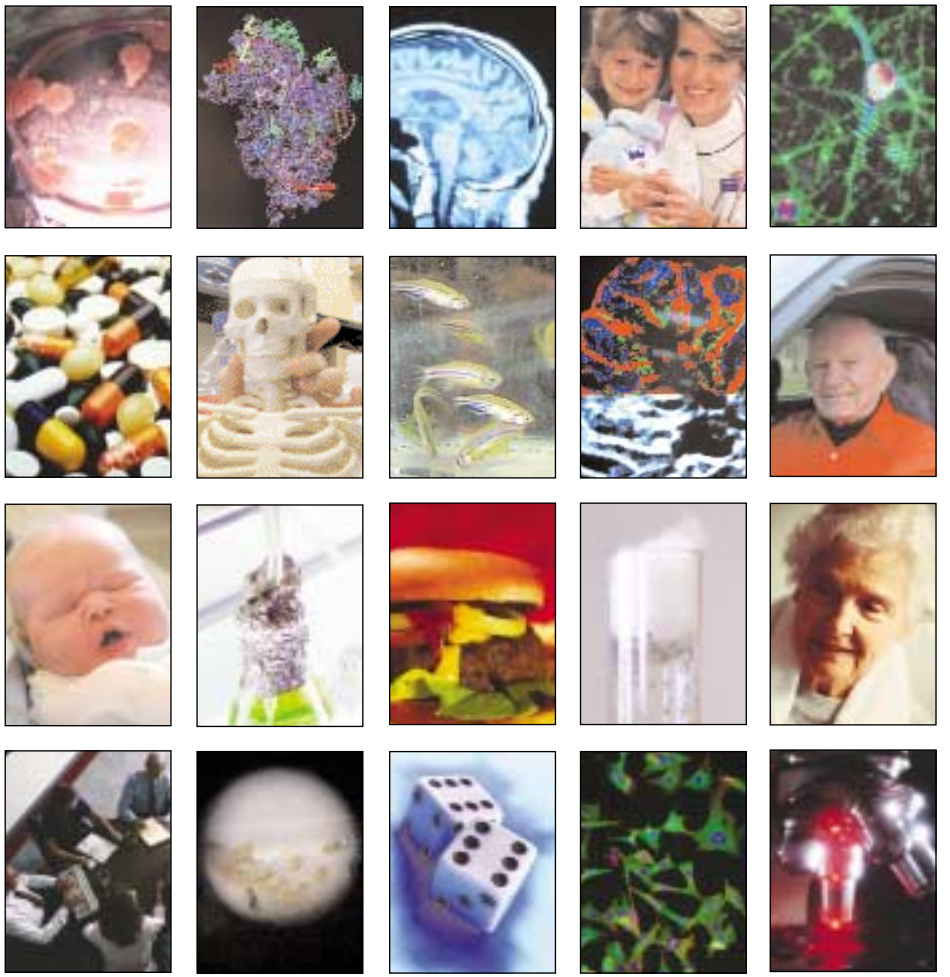
A Passion



for Discovery

THE DONAGHUE INVESTIGATOR PROGRAM
THE PATRICK AND CATHERINE WELDON DONAGHUE MEDICAL RESEARCH FOUNDATION

The Donaghue Investigator Program

A Passion for Discovery

THE FIRST FIVE YEARS
1998–2002

THE DONAGHUE INVESTIGATOR PROGRAM
THE PATRICK AND CATHERINE WELDON DONAGHUE MEDICAL RESEARCH FOUNDATION

The Donaghue Investigator Program

The Donaghue Investigator Program in Health-Related Research, established in 1998, supports particularly promising medical researchers holding faculty appointments at Connecticut institutions. Since the program emphasis is upon the researcher rather than upon a specific research project, Investigators are given wide latitude to pursue studies in promising areas.

The Donaghue Investigator program is funded by the Patrick and Catherine Weldon Donaghue Medical Research Foundation, established by the will of Ethel F. Donaghue. One of Connecticut's first woman lawyers, Miss Donaghue, who died in West Hartford in 1989, directed that the charitable trust of more than $50 million named for her parents be created to carry out medical research of practical benefit to human life.

Since its inception, the Donaghue Investigator program has accounted for approximately 25 percent of the Foundation's awards. For the past five years, an average of four awards of $100,000 per year for five years have been granted to researchers who have demonstrated exceptional potential for an outstanding independent research career. The Trustees look for leaders active across a broad spectrum of research fields, particularly those involving studies that focus on the prevention and alleviation of human suffering.

Investigators are selected not only for their sound scientific methodology and creativity in research, but also for their aptitude and willingness to connect their research to clinical practice. Like all Donaghue Foundation awards, each project must have practical benefit in the near future.

The Foundation accepts Donaghue Investigator research grant applications only from within Connecticut. Particularly welcome are projects of potential benefit to the people of the Hartford area, the source of the Donaghue fortune. The Foundation is especially interested in research that will benefit the poor, the elderly, or the disadvantaged. Twenty scientists received support from the Donaghue Investigator program between 1998 and 2002.

In selecting Donaghue Investigators over the past five years, the Trustees have assembled a diverse group of institutions, research interests, and academic disciplines. For 2003, the Trustees are particularly interested in receiving applications from scientists studying pain management, patient safety, injury prevention, and the ethics of health care.

Donaghue Investigators By Year

1998

Stephen H. Devoto, Ph.D., Wesleyan University
Mark B. Gerstein, Ph.D., Yale University
Sharon K. Inouye, M.D., M.P.H., Yale University School of Medicine
Zeev N. Kain, M.D., Yale University School of Medicine
David L. Rimm, M.D., Ph.D., Yale University School of Medicine
Stephen M. Strittmatter, M.D., Ph.D., Yale University School of Medicine

1999

Carlos Grilo, Ph.D., Yale University School of Medicine
Stephen Helfand, M.D., University of Connecticut Health Center
Scott Rivkees, M.D., Yale University School of Medicine
Joann Sweasy, Ph.D., Yale University School of Medicine

2000

Sandra Hewett, Ph.D., University of Connecticut Health Center
Stephen King, Ph.D., University of Connecticut Health Center
Ishita Mukerji, Ph.D., Wesleyan University
Nancy Petry, Ph.D., University of Connecticut Health Center

2001

Richard Marottoli, M.D., M.P.H., Yale University School of Medicine
Carol Pilbeam, Ph.D., M.D., University of Connecticut Health Center
Robert Reenan, Ph.D., University of Connecticut Health Center

2002

Elizabeth Bradley, Ph.D., Yale University School of Medicine
Kevin Claffey, Ph.D., University of Connecticut Health Center
Barbara Kazmierczak, M.D., Ph.D., Yale University School of Medicine

Fish Tales and Hedgehog Signalling

1998
Stephen H. Devoto, Ph.D.

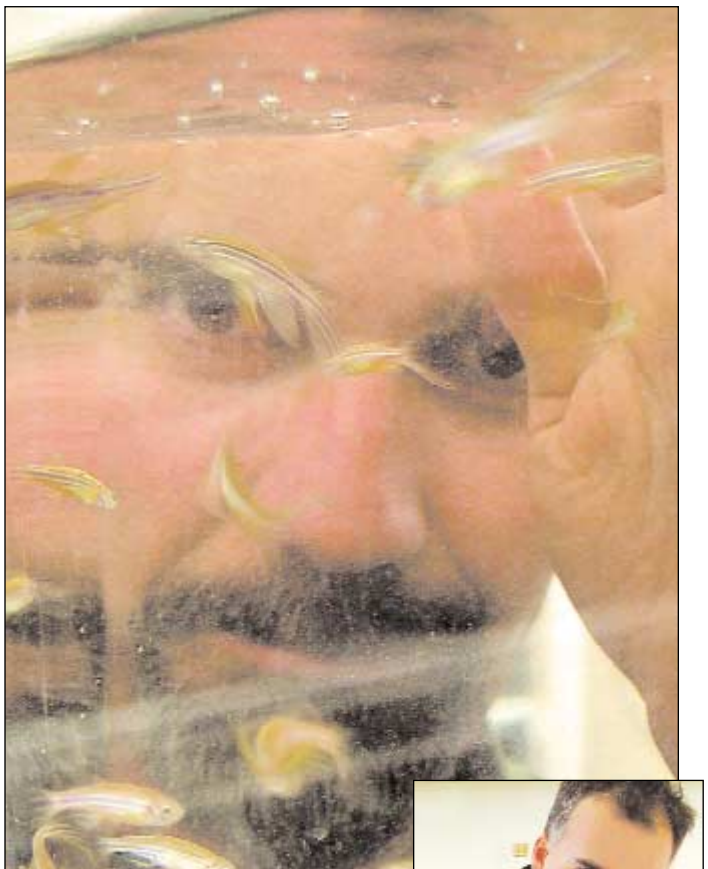
Peering into bubbling tanks of baby zebrafish, those ubiquitous black-and-white striped denizens of tropical aquariums, Stephen Devoto, Ph.D., scrutinizes the skeletal muscles of the tiny vertebrates. Muscle fibers in fish are either "fast" or "slow," depending on whether they power a swift getaway from a predator or steady cruising through water. By studying muscular development in mutant strains of zebrafish, Dr. Devoto hopes someday to elucidate the genetic errors that lead to human heart disease, birth defects and muscular dystrophy.

In humans, abnormal genes cause various types of muscular dystrophy, which strikes one in 4,000 Americans, almost exclusively boys, between the ages of two and six. "Muscular dystrophy typically paralyzes boys by elementary school and kills them before they reach their twenties," he says. "It's particularly tragic because they're healthy in every other way." He is confident that understanding the genes involved in zebrafish muscle development will rapidly lead to an understanding of the genes that are defective in muscular dystrophy.

What triggers the growth of muscle fibers? When do slow and fast muscles differentiate? Why does muscle development sometimes go awry? Mutant zebrafish who lack a gene to develop slow muscles may hold the key to understanding muscular dystrophy and developing the best possible treatments for these diseases. By manipulating cells in experimental embryos smaller than a fingernail, Dr. Devoto has identified a gene in the tiny translucent fish that is also required for muscle development in humans.

Dr. Devoto has shown that slow muscle fibers arise very early in vertebrate development—at about 24 hours in zebrafish or within the first six weeks of human pregnancy. One or more Hedgehog genes—named for the video game character *Sonic Hedgehog*—signal development of two specific types of slow muscle fibers. "Our biggest discovery has been that there are two ways to make muscle—and that different genes are involved," says Dr. Devoto.

In 1997, Dr. Devoto traveled cross-country from the University of Oregon with a bird, a cat, and 300 zebrafish in a U-Haul truck. Today, row upon row of plastic fish tanks have taken over his lab at Wesleyan University, where he teaches one course each semester as an assistant professor of biology. He bicycles to work, enjoys high-altitude mountain climbing, and raises chickens on a five-acre farm with his wife and two children. "The five-year grant from the Donaghue Investigator Program in 1998 provided me with seed money that has led to additional funding from the National Institutes of Health," he says. "It's given me the freedom and security to pursue the challenge and discovery of pure research."



Above, Stephen H. Devoto, Ph.D., keeps his eye on his experimental zebrafish. Dr. Devoto oversees more than 3,000 of the miniscule vertebrates, which range in size from a few millimeters to a couple of inches in length.

1998
Mark B. Gerstein, Ph.D.

Deciphering the Twisted Code

Mark B. Gerstein, Ph.D., analyzes the geometry of proteins, rotating structures in three-dimensional color to reveal genome sequences and macromolecular structures of proteins—the new field of bioinformatics.

The human genome comprises about 30,000 genes that code for a million or more different proteins—the biochemical powerhouses of the body. Three billion or so DNA base pairs serve as templates for a staggering array of proteins, molecular machines that enable organisms to survive and reproduce. The recent unraveling of the DNA blueprint for the human genetic code has spawned the science of *comparative genomics*. With support from the Donaghue Foundation over the past five years, Mark B. Gerstein, Ph.D., has analyzed not only the human genome, but also gene sequences and protein structures in microbial genomes—the genetic maps of invisible life forms whose evolutionary diversity spans millennia.

"We compare genomes in terms of protein folds, biochemical pathways, and patterns of gene expression," explains Dr. Gerstein, who since being named a Donaghue Investigator has been promoted to associate professor of molecular biophysics and biochemistry with tenure at Yale University. "We are also developing methods to cluster proteins into fold families and predict structure and function from sequence similarity."

Drawing on the enormous computing power of huge computational databases, Dr. Gerstein analyzes the geometry of proteins to reveal genome sequences and macromolecular structures of proteins—the new field of *bioinformatics.* Though bacteria share a surprising number of genes with humans, syphilis-causing *spirochetes* or Lyme disease pathogens contain distinctive gene sequences that may someday be disrupted with "designer" antibiotics. "Imagine that you wanted to design a drug to attack the proteins of a microorganism," says Dr. Gerstein. "You'd look for a protein target that didn't have close relatives in the human genome."

Within chromosomes lie *pseudogenes*, sequences of genomic DNA that are so similar to normal genes that they are regarded as non-functional copies or close relatives of genes. Arising during duplication or as transcription errors, these mutations, insertions, deletions, or frame shifts alter the DNA sequence of a gene. Where do these "dead" genes come from? What purpose do they serve? Are they remnants of an evolutionary pathway that didn't pan out, some sort of mysterious protein fossils?

"Eventually, we would like to compare the human proteome against those of pathogens and identify unique pathogen proteins as antibiotic targets," he says. Although Dr. Gerstein's lab has contributed to annotating the human genome and built tools useful to the pharmaceutical industry, the payoff in terms of marketable drugs may take decades, he warns. "I'm not a Lone Ranger scientist—biomedical research is a team effort."

Hospitals May Be Hazardous

1998
Sharon K. Inouye, M.D., M.P.H.

Hospitalization all too often plunges the elderly into a terrifying haze of delirium. For more than two million patients each year, admission to a hospital brings a long downward spiral into confusion, at a cost to Medicare of more than $8 billion annually. Diagnostic tests, treatments, and medications—even high levels of activity and noise at night—place seniors at high risk for acute cognitive and functional decline.

"Hospital care is inherently hazardous for older people," explains Sharon Inouye, M.D., M.P.H., professor of medicine (geriatrics) at Yale School of Medicine, whose husband is Donaghue Investigator Stephen Helfand, M.D. "The longer elderly patients stay in the hospital, the greater their risk for delirium."

Dr. Inouye's groundbreaking research led to the Hospital Elder Life Program (HELP), a set of six interventions aimed at preventing cognitive decline in seniors. Elderly patients often struggle with vision or hearing loss and are at higher risk for dehydration, sleep deprivation, cognitive impairment or immobility, which together with medications may bring on delirium in a hospital setting. Can something as simple as giving an elderly patient a glass of warm milk instead of a sleeping pill prevent disorientation?

"We found that HELP reduces the chances of developing delirium by 40 percent," says Dr. Inouye, whose findings are being adopted in hospitals across the country. "Nurses, doctors, and trained volunteers help patients get reoriented three times a day, make them get up and walk three times a day or perform range of motion exercises if they're confined to bed. It has been so successful that now patients in the Emergency Room are refusing to be admitted when they find out they're not being sent to an Elder Life floor!"

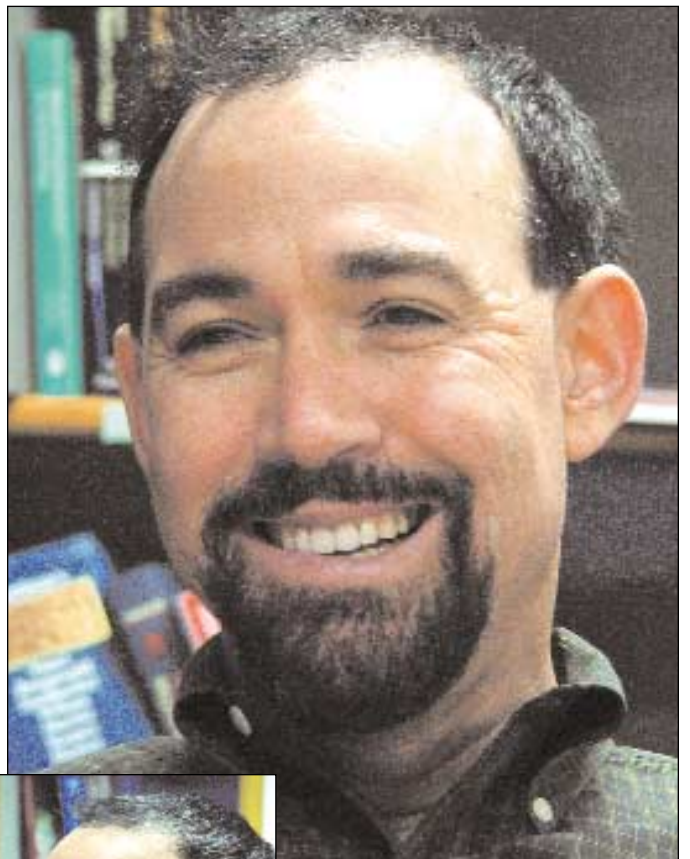
With Donaghue grant support, Dr. Inouye has studied the recognition, prevention, outcomes, and health policy implications of delirium. "The tremendous flexibility of the Donaghue grant gave me the power and freedom to move both my research and my career ahead," says Dr. Inouye, one of only a handful of women doing patient-centered research to be promoted to full professor with tenure at Yale School of Medicine.

She has been published widely and recognized with numerous awards. A voracious reader and mother of two sons, she is a fourth-generation Japanese-American from a long line of physicians, but once seriously considered becoming a classical harpsichordist. "Eventually I decided a musical career was selfish," she recalls, "I wouldn't be helping the world or humanity. I can't think of a way to do more good than through medicine."

"I couldn't have done this work without Donaghue funding," says Sharon K. Inouye, M.D., M.P.H., as she details the many studies she has conducted as a Donaghue Investigator, recently including SPECT scans.

1998
Zeev N. Kain, M.D.

Kid Fears: Anesthesia Anxiety



Zeev N. Kain, M.D., medical director of the Pediatric Surgery Center at Yale-New Haven Hospital, says giving children a flavored sedative 20 minutes before surgery can relax them so much that they forget the whole experience.

Children who sob with terror as they're sinking under anesthesia not only may have nightmares for weeks or months afterward, but heal more slowly than calmer kids. All too often, an anesthesiologist presses a smelly gas-filled mask over a screaming child's face until the struggling stops. Doctors operate on about three million children each year in the United States, but only a fraction receive a sedative before surgery.

"Up to two-thirds of children—especially those too young to understand what's happening—experience high anxiety before an operation," says Zeev Kain, M.D., director of pediatric anesthesiology at Yale-New Haven Hospital and professor of child psychiatry at Yale School of Medicine. "Much of the anxiety can be explained by the fact that the majority of kids are taken into the operating room awake, alone, and crying."

Children wheeled by masked strangers into a surgical theater are far less terrified when a parent is allowed to go along and hug them as they fall asleep, which is the practice at Yale-New Haven Hospital.

"Simply dimming lights or playing soft classical music in the operating room can help reduce anxiety levels and improve outcomes," says Dr. Kain, whose early grant from the Donaghue Investigator program has led to $3.5 million in additional funding from the National Institutes of Health. "Donaghue funding allowed me to investigate non-traditional approaches like ear acupuncture and music therapy—roads not traveled before."

Dr. Kain, who was born in Israel, has been promoted to tenured professor and medical director of the Pediatric Surgery Center at Yale-New Haven Hospital since winning the Donaghue grant in 1998. He began his research by measuring levels of the fear-linked hormone cortisol in the blood, and has shown how disturbed sleep, nightmares, bedwetting, loss of appetite, and behavioral changes commonly afflict children after surgery.

Although some hospitals still ban parents, surveys show more moms and dads are now making the journey into surgical suites with their kids. "It may be presumptuous of us, but I like to think that the work we've done is making a difference because we've actually measured the impact of anxiety on recovery."

How can doctors help parents control their own fears so they don't unwittingly make their children more nervous? "When my older daughter had surgery two years ago, my wife went with her into the operating room and I stayed outside," says Dr. Kain. "It's a lot different when it's your own child."

Predicting Outcome in Breast Cancer

1998
David L. Rimm, M.D.

Connecticut claims the dubious distinction of the highest rates of breast cancer in the country, according to the American Cancer Society. Nationally, breast cancer will strike more than 200,000 times this year and take more than 40,000 lives.

"Different cancers have different biological behaviors," explains David Rimm, M.D., Ph.D., an associate professor of pathology at Yale University School of Medicine. "Even in node-negative cancers, there are menacing cells circulating through the blood that we can now characterize with molecular technology and microscopy."

Proteins implicated in breast cancer include enzymes, growth factors, receptors, cell cycle regulators, and adhesion molecules. A measurement of expression of some of these proteins offers potential "practical benefit" as targets for diagnostic or therapeutic anti-cancer strategies.

Dr. Rimm is examining archived malignant tissue with microarrays, which allow study of hundreds of samples at once. New quantitative tissue immunoassay techniques permit superb accuracy without destroying specimens. "Discovery of biological tools to characterize breast cancer will potentially allow us to develop new tests to classify tumors using biological markers," explains Dr. Rimm, who received his Donaghue Investigator grant in 1998 to study adhesion protein expression as a predictor of metastasis in both breast cancer and melanoma. "We've found that molecular changes are more subtle in melanoma, but we are gearing up to participate, as the bio-specific diagnostic part, of new clinical trials related to two or three medications for breast cancer."

Dr. Rimm has two aunts and a cousin who were victims of breast cancer, giving a very personal motivation to his efforts. He has worked with breast cancer survivors in grassroots organizations and volunteered as a grant reviewer with the Komen (Breast Cancer) Foundation and the Connecticut Breast Cancer Alliance.

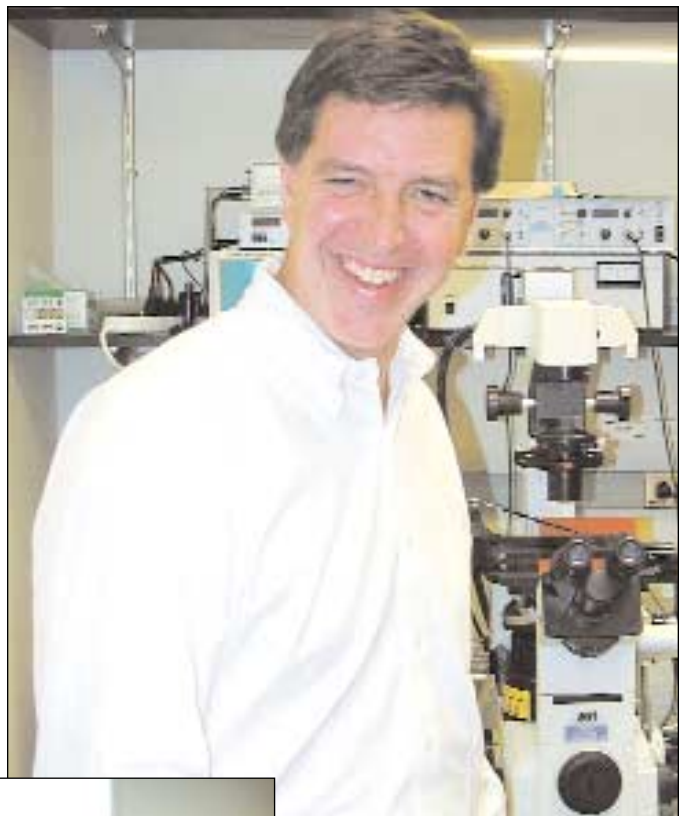
"I believe pathology is still largely practiced as it was 50 years ago," asserts Dr. Rimm, who applies his expertise in cellular biology and spectral analysis to research, while spending one-quarter of his time in clinical practice.

"Funding from the Donaghue Foundation allowed me to apply quantitative molecular tools to assessing metastasis risk and predicting responses to cancer therapy. I hope we are soon able to use these tools to predict response to therapy for breast cancer patients right here in Connecticut."

David Rimm, M.D., Ph.D., associate professor of pathology at Yale School of Medicine, directs the Yale Cancer Center/Pathology Tissue Microarray Facility and collaborates with other Yale researchers in a commercial venture, a digital pathology company called Histometrix.

1998
Stephen M. Strittmatter, M.D., Ph.D.

Nogo: Axons Don't Regrow



Stephen M Strittmatter, M.D., Ph.D., Vincent Coates Professor of Neurology at Yale University School of Medicine, is leading a research project that resulted in the discovery of the Nogo protein, which prevents the regeneration of axons after traumatic injury to the spinal cord.

In 1995, actor Christopher Reeve, best known for his movie role of Superman, was thrown from his horse at an equestrian event, crushing his cervical vertebrae just below the brain stem. As he continued to act, broken in body but not in spirit, many Americans saw firsthand the devastating results of spinal cord injury.

What if we could regrow the fibers, up to a meter in length, that connect the brain to the nerve centers of the spine? Unlike reptiles, humans don't regenerate nerves in the brain and spinal cord. The neuron's powerhouse is the axon, from which radiate long, threadlike strands. Neurotransmitters smooth the biochemical pathway as axons fire and impulses jump the synapses between nerve cells. Infinitesimal threadlike strands of fiber carry lightning-fast messages from the cerebral cortex to the muscles, allowing coordination of complex movements.

"About five years ago there was an explosion of knowledge about axon growth in developing brains," says Stephen Strittmatter, M.D., Ph.D., Vincent Coates Professor of Neurology at Yale University School of Medicine. "I began to wonder how we could grow and repair axons after someone had suffered damage to the central nervous system. What we discovered was that there are axon inhibitors in the adult brain. It's not just that axons can't grow—a protein called 'Nogo' actually prevents them from regenerating after a spinal cord injury."

Why do adults lose the *plasticity* that allows children to grow new brain cells? During development—up to adolescence—brain cells continue to grow, but then they stop, which stabilizes the synapses, explains Dr. Strittmatter. Married and the father of four children, he enjoys skiing and sailing with his family when he's not in the lab.

His early work as a Donaghue Investigator in 1998 spurred research that is now supported by the National Institutes of Health and the Christopher Reeve Paralysis Foundation, among others. Though doctors believed the quadriplegic actor had permanently lost all feeling in his legs and arms, as well as his ability to breathe, he has regained some sensation and can now breathe on his own for up to 90 minutes. "It's difficult to get funding to study an open-ended idea that may someday have 'practical benefit' for human health," says Dr. Strittmatter, whose research has won worldwide recognition since the discovery of the Nogo protein. "People were much more skeptical then. The Donaghue Investigator award gave us our start."

Obesity and Binge Eating

1999
Carlos Grilo, Ph.D.

Recent research shows that roughly 60 percent of Americans are overweight and many of them are considered obese. "There's been an alarming increase in obesity over the past few decades," says Carlos Grilo, Ph.D., a clinical psychologist and associate professor of psychiatry at the Yale School of Medicine. "Obesity is a major, growing public health problem. Associated medical problems, such as diabetes, heart disease, and certain cancers are on the rise, while health care costs have been expanding along with waistlines."

Dr. Grilo's research program focuses on understanding the needs of a subgroup of obese persons who binge eat. While overeating and inactivity account for weight gain, a substantial group of obese people also suffers from binge eating. Binge eating—consuming unusually large amounts of food while experiencing a clear loss of control over the eating—is found in about a quarter of obese people.

Dr. Grilo's research has focused on understanding the behavioral, psychological, cultural, and treatment needs of binge eaters. Unlike other eating disorders such as *anorexia nervosa* and *bulimia nervosa*, binge eating afflicts both men and women well into and throughout adulthood and is also widespread in persons of color and of all socioeconomic groups. People who binge eat are substantially more likely to also have greater body dissatisfaction and higher rates of psychological difficulties, such as depression, than their obese peers who do not binge eat.

"The Donaghue Investigator program has enabled me to conduct a series of studies that have fairly immediate 'practical benefit' for binge eaters," says Dr. Grilo. The most important study addresses the practical issue of the best and most effective way to treat binge eating. "With Donaghue funding, we're comparing a behavioral/lifestyle weight loss program with cognitive behavioral therapy. There's impressive support for a specific treatment approach called cognitive behavioral therapy, although few practitioners in New England are trained to provide it. Our study uses self-help manuals that provide step-by-step advice directly to patients with only minimal guidance from clinicians. We are helping patients to become their own therapists so they can change their thinking and gain control over their eating."

"The Donaghue grant has given me the freedom to explore promising new treatments," says Dr. Grilo, director of psychology at the Yale Psychiatric Institute, whose passions include travel and enjoying different cuisines with his wife of 18 years and their two daughters. "Despite my profession, I believe eating can be an art form."

Carlos Grilo, Ph.D., is using funding from the Donaghue Investigators program to compare a good behavioral weight loss program with cognitive behavioral therapy to treat binge eating, which refers to eating unusually large amounts of food while experiencing a clear loss of control over the eating.

1999
Stephen Helfand, M.D.

Fruit Flies Buzz: "I'm Not Dead Yet!"

Above, Stephen Helfand, M.D., eyes a test tube of fruit flies with the Indy *(I'm Not Dead Yet) gene mutation that can double the average lifespan of a fruit fly. Female Indy flies deprived of food lay fewer eggs than non-Indy females, perhaps explaining why long-lived mutants haven't overtaken the world.*

When his second son was born with a lethal developmental disorder, Stephen Helfand, M.D., watched in vain as the devastating neurological disease overcame his son before his third birthday. "I stopped wanting to work in neurobiology," Dr. Helfand says. At the urging of his wife, geriatrician Sharon K. Inouye, M.D.—a 1998 Donaghue Investigator—he switched to the biology of aging.

"I had already discovered the power of genetics, particularly using the fruit fly model," says Dr. Helfand, whose research at the University of Connecticut Health Center involves the fruit fly, *Drosophila melanogaster.* "During my postdoctoral fellowship at Stanford I realized that this powerful system could be used to explore the biology and genetics of aging. The fruit fly had already been used to unlock the mysteries of development—how you go from a single fertilized egg to a mature individual—and I thought that it could be used to do the same for aging. What I found was that despite the aging process being one of the most important to all of us, many of the assumptions we make about it may be false. This opened up the possibility of novel approaches, such as using molecular genetics in the fruit fly, to help understand aging in humans."

What can genetically manipulated flies teach us about aging? Can we tinker with our genes and triple our lifespan? Why do we die? Do we have to?

In *Monty Python and the Holy Grail*, a plague victim cries, "I'm not dead yet!" as he's carted off prematurely. Dr. Helfand's team has discovered a gene in the fruit fly that can double its average lifespan, and named it *Indy*, short for the eponymous I'm Not Dead Yet.

Why do all Indy mutants live up to twice as long as normal flies? The answer seems to be that the Indy gene codes for a protein that transports nutrients across the plasma membrane into cells essential for metabolism. In mammals these membrane tranporters are found in cells in the digestive tract, placenta, liver, kidney, and brain. While the precise anti-aging mechanism is unknown, he believes that the rejuvenating gene seems to regulate energy and may mimic the effects of caloric restriction, known to extend lifespan.

"The Donaghue Investigator program allows us to think and explore in ways a traditional grant would never allow," says Dr. Helfand. Compelling evidence contradicts the conventional thinking that the price for multicellular life is inevitable decline over time. "We are not enslaved by our genetics," says Dr. Helfand. "There's no law that says just because we're living we have to decline with age."

At Risk for Brain Injury

1999
Scott Rivkees, M.D.

Each year, 10,000 premature babies in Connecticut suffer neonatal brain injury. Low-birthweight infants born at less than 32 weeks are most likely to be affected. As women wait longer to have children, the incidence of so-called " white matter disease" in premature infants is on the rise, since advanced maternal age is a contributing factor. Fertility drugs causing multiple births, medical problems *in utero*, and maternal illness also raise the risk of brain injury.

"Each year for the past five years the incidence of brain injury in premature infants has increased," says Scott A. Rivkees, M.D., associate professor of pediatrics at the Yale School of Medicine. "Babies weighing less than one kilogram—2.2 pounds—are surviving. Tremendous advances have occurred in neonatology, bringing better nutritional support, new medications, and recognition and treatment of infections. Now we are trying to find pharmacological ways to prevent brain damage in these at-risk infants."

Although the term "white matter injury" persists, the condition is now known to affect not just nerve fibers, but "grey matter" as well. A neurochemical called *adenosine*, which has a devastating effect on developing nerve cells, has been linked to brain injury and mental retardation in these infants. Adenosine receptors present on nerve cells are activated when adenosine levels rise under the kind of stress that afflicts premature newborns.

Using transgenic mice, Dr. Rivkees team is experimenting on nerve cells with adenosine antagonists—drugs that block the deleterious action of the chemical on the developing brain. Because neonatal brain injury is linked to poor blood flow—resulting in lack of oxygen—he is treating hypoxic (oxygen-starved) mice with adenosine antagonists to see if he can prevent brain injury. Next will come primate studies, and eventually clinical trials, if all goes well. Caffeine—a common non-selective adenosine antagonist—is used to stimulate respiration. Is it completely safe for infants? Is there a more selective drug that could target specific receptors in the brain?

Dr. Rivkees is working with U.S. Senator Christopher Dodd's Children and Families Senate Subcommittee to help draft legislation to expand newborn screening programs. He testified before Congress last year and helped draft the proposed "Newborn Screening Saves Lives" Act. The father of two sons, he is a runner who loves the outdoors and raises champion Sevastopol geese.

"In Connecticut, nine percent of all births are premature," he says. "Support from the Donaghue Foundation has allowed us to develop a new line of research to safeguard the lives of these children."

Scott A. Rivkees, M.D., associate professor of pediatrics at the Yale School of Medicine, and director of the Yale Child Health Research Center, is seeking pharmacological interventions to prevent brain damage in premature infants.

1999
Joann Sweasy, Ph.D.

Meiotic Mutations and Cancer Clues

Joann Sweasy, Ph.D., is investigating the hypothesis that glutamate receptor interacting protein 1 (GRIP1) acts as a scaffold for cellular trafficking of proteins.

When Joann Sweasy, Ph.D., was a child, her four-year-old cousin died of leukemia, which, combined with a passion for science, shaped her future career. "I'm studying the relationship between mutations and cancer," explains Dr. Sweasy, whose lab in the Department of Therapeutic Radiology at Yale University School of Medicine is researching the workings of an enzyme called DNA polymerase beta in mutagenesis. In the long run, we'll understand how mutations originate during meiosis—in the earliest stages of germ cell division."

Why do mutations arise in DNA? How are diseases inherited? How do seemingly negligible DNA synthesis errors predispose someone to developing cancer later in life?

"DNA polymerase beta is sloppy," says Dr. Sweasy, an associate professor of therapeutic radiology and genetics. "When copying DNA it makes a lot of mistakes that could be the source of mutations. For example, a friend of mine has Lou Gehrig's Disease, or ALS, which may have a mutational basis in meiosis. We're asking fundamental questions about mutations to see how cellular changes may predispose people to a mutagenic process leading to cancer or other diseases."

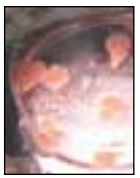
Dr. Sweasy is analyzing the role of DNA polymerase beta and its associated proteins during meiosis by studying "transgenic" mice whose genes have been manipulated to create mutations. Mice technology allows Dr. Sweasy's team to isolate spermatocytes undergoing meiosis, which can be studied in vitro. Mutant proteins identified with genetic screening are analyzed using kinetics to understand the mechanisms polymerase beta employs to synthesize DNA accurately.

'Eventually we'll understand how mutations arise in DNA," asserts Dr. Sweasy, who is married with a daughter adopted from China. She is active in the Women in Science outreach program, which encourages women of all ages to consider careers in science. "At Yale, many young women are conflicted about balancing career and family. Look at the low numbers of women in the tenured ranks. I'm lucky to have established my lab before my daughter arrived.

"The Donaghue Investigator Program provided me with initial funding despite the fact that I had no track record in this area of research," says Dr. Sweasy. "I would not have been able to perform any of the studies without the Donaghue support. Unlike most grants that invest in a project, the Donaghue invests in the person. The 'practical benefit' may come from the Investigators themselves—or their scientific offspring—students or those who work in their labs whose careers will bring remarkable discoveries."

COX-2 and "Stroke In A Dish"

2000
Sandra Hewett, Ph.D.



Each year more than 700,000 Americans suffer a stroke, the leading cause of disability in adults and the third leading cause of death. A stroke causes devastating—and often irreparable—injury to brain cells by disrupting cerebral blood flow.

Sudden weakness or paralysis, particularly on one side, distorted vision and disjointed speech often signal the onset of a stroke. Treatment is limited to "clot-busting" drugs that must be administered within the first three hours following the onset of stroke symptoms. After that, the therapy can do more harm than good.

"Currently there are no approved medications to offer protection of at-risk tissue after a stroke," says Sandra J. Hewett, Ph.D., a neuropharmacologist at the University of Connecticut Health Center whose goal is to develop drugs to prevent damage caused by a blood clot in the brain. "We focus on the 'walking wounded' cells outside the main core of damage that are destined either to live or to die," she says. "If we can interfere with the mechanism that causes these cells to die, we might be able to figure out how to lessen stroke damage."

One way to study this is to induce chemical reactions in an *in vitro* cell culture preparation—what Dr. Hewett irreverently refers to as "stroke in a dish"—and test various drug combinations for their ability to prevent injury. Recently, her lab has demonstrated the ability of certain nonsteroidal anti-inflammatory drugs (NSAIDs)—including ones commonly marketed under the brand names such as Naproxen or Aleve—to inhibit brain injury in this in vitro preparation, as well as in an animal model. NSAIDs inhibit the function of cellular proteins known as *cyclooxygenases.*

"Our research convincingly shows that an enzyme called cyclooxygenase-2—COX-2 for short—likely contributes to the evolution of brain injury in the aftermath of a stroke," she explains. How does the COX-2 enzyme work? How is it regulated? What triggers the protein synthesis that ultimately damages the brain? How can the therapeutic time window be extended? She hopes to answer these questions working in collaboration with her husband, Dr. Jim Hewett, a molecular biologist with a lab just down the hall at the UConn Health Center. Together they have received a joint grant from the National Institutes of Health (NIH) to explore the workings of the COX-2 enzyme in brain.

When the Drs. Hewett are not working in the lab, they enjoy working on their home and outdoor sports like hiking, snowshoeing, and skiing. Together they have traveled to India and trekked the mountains of Nepal.

"We began this research with Donaghue funding, but now the NIH is supporting it," says Dr. Hewett."Because the Donaghue Foundation funds people of promise in mid-career, giving them the flexibility to go in a direction they might otherwise not be able to pursue, we were able to explore this potentially important avenue of investigation."

2000
Stephen King, Ph.D.

Molecular Motors Power Cell Life

Stephen M. King, Ph.D., associate professor of biochemistry at the University of Connecticut Health Center, is unlocking the process of cellular transport. Chlamydomonas reinhardtii, a unicellular green alga, provides a model system for Dr. King's study of motility, dynein structure and function, and molecular genetics.

Protein motors that provide the driving force for intracellular transport fascinate Donaghue Investigator Stephen King, Ph.D., associate professor of biochemistry at the University of Connecticut Health Center. Unlocking the mysteries of cellular movement has broad application to fundamental processes. His research into how molecular motors power such vital activities as cell division and motility may someday be of value in treating disorders such as cancer, male infertility, and blindness.

"Identifying specific protein cargos helps us understand the mechanism that allows a virus like Hepatitis B to replicate in cells," explains Dr. King, who is seeking to elucidate how viruses utilize the molecular transport system of the host cell in order to replicate and establish a productive infection. "Certain viral proteins disrupt cytoplasmic functions and 'hijack' the cellular transport machinery."

How do proteins translate chemical energy into mechanical energy within the cell? How does a molecular motor attach to a specific cellular cargo? What mechanism directs the cargo to its correct cellular location?

Dynein microtubule motors are cellular complexes that contain multiple distinct protein components. Dr. King hypothesizes that key motor-cargo interactions within the cell are mediated, and perhaps controlled, by these molecules. Attaching individual molecular motors to the proper cellular cargos involves multiple enzymes, which must be precisely controlled to ensure the proper functioning of complex cellular systems. When the signals that control the transport system go awry, cancer, for example, may arise as the result of uncontrolled mitoses. Dynein is also involved in the motility of cilia and flagella, and as such plays an essential role in fertilization, development, mucus transport, and other key cellular processes. *Chlamydomonas reinhardtii*, a unicellular green alga, provides a model system for Dr. King's study of motility, dynein structure and function, and molecular genetics.

With Donaghue support, Dr. King spent two years in an effort to identify candidate cargo proteins and investigated how motors are involved in mitochondrial biosynthesis. Since molecular transport is fundamental to normal cellular function, disruption of the regulatory mechanisms can have profound implications for cell viability. "Support from the Donaghue Foundation allowed me to get the lab up and running," says Dr. King, who was born and educated in England. "Based on that work, I have received additional funding from the National Institutes of Health. We're beginning to understand basic cellular mechanisms that power complex motor functions, which will someday have enormous 'practical benefit' in the treatment of disease."

Sickle Cell Fiber Formation

2000
Ishita Mukerji, Ph.D.

Sickle cell disease, the most common inherited blood disorder in America, is a molecular disease that results from the mutation of a single amino acid in the hemoglobin protein. Substitution of the amino acid valine for glutamic acid in the abnormal hemoglobin S molecule makes red blood cells hard, sticky, and misshapen, leading to painful anemia. African-Americans are particularly affected by the disease, caused by a recessive gene, which protects against malaria in heterozygous individuals.

"By studying the structure and energetics of sickle cell hemoglobin fibers, our goal is to elucidate the mechanism of sickle cell hemoglobin fiber formation," explains Ishita Mukerji, Ph.D., associate professor of molecular biology and biochemistry at Wesleyan University. "At the most basic level, we are interested in figuring out how and when fibers are formed, as well as assessing the effectiveness of different inhibitors."

What causes aggregation of proteins into fibrils? How can a single mutation in a gene sequence lead to non-functional protein assembly? What drugs can be designed to disrupt the defective process? Once researchers understand the faulty mechanism, they can begin to design more effective agents to inhibit fiber formation and disrupt fibers. Even large proteins can be examined with a technique called Raman spectroscopy, which utilizes light scattering to gain information about a molecule's "vibrations."

"You can't predict the shape and structure of a protein from its gene sequence," says Dr. Mukerji. "By studying the proteins themselves, we hope eventually to design drug therapies for these diseases." Outreach to the sickle cell community of sufferers and scientists is an important part of Dr. Mukerji's mission as a Donaghue Investigator. With the help of her students, she has created a website, www.sicklecellinfo.net, that reports on research activities in her lab and provides links to other sites. "Most sickle cell websites focus on treatments," she explains. "Ours concentrates on the hemoglobin molecule."

Dr. Mukerji, whose parents came to the United States from India, has been promoted to associate professor since being named a Donaghue Investigator. Married with two young children, she is active in networking efforts to improve childcare at scientific conferences. A member of the prestigious Biophysical Society, she chairs the committee on professional opportunities for women.

"It has been a luxury to have so much flexibility in funding," says Dr. Mukerji. "We can branch out and explore other proteins. Research into fiber formation may someday be of 'practical benefit' not only for sickle cell disease, but also for 'Mad Cow' and Alzheimer's disease."

Outreach to the sickle cell community of sufferers and scientists is an important part of Dr. Mukerji's mission as a Donaghue Investigator. With the help of her students, she has created a website, www.sicklecellinfo.net.

2000
Nancy Petry, Ph.D.

Odds Are Good for Problem Gamblers

Dr. Petry studies adults who gamble frequently but do not have severe gambling problems. She relies primarily on media advertising to recruit self-identified study participants, and with the agreement of the casino, was able to screen passing gamblers at the Mohegan Sun last summer.

Gambling can be so seductive that it can snare its victims in a stranglehold of addiction, leaving them remorseful and bankrupt. The estimated $50 billion that American gamblers spend on legal wagering each year can lead to problems other than simply losing a bet.

"Some people who gamble often but who are not compulsive gamblers still want to reduce or quit," explains psychologist Nancy Petry, Ph.D., an associate professor at the University of Connecticut Health Center whose research involves behavioral treatments for addictive disorders. Dr. Petry studies adults who gamble frequently but do not have severe gambling problems. "They may not gamble enough to lose everything, but they may spend more than they want or have a spouse who is becoming increasingly critical of their behavior."

Gamblers may receive one of three brief targeted interventions lasting from one to four sessions. Participants are randomly assigned to one of four groups. One group is followed for nine months without treatment, while another meets with staff for five minutes to review ways to reduce gambling. The third group gets one 50-minute motivational interview and the fourth an intensive educational program with three follow-up meetings.

How well do interventions work? What makes gamblers forget how often and how much they lose? Do regular gamblers develop more severe gambling problems or psychiatric illnesses down the road? Why do so many also suffer from substance abuse or other addictions?

"Escape from boredom is the reason why some people gamble, and for others, it may be the excitement or the lure of a big win," notes Dr. Petry. "We help gamblers learn more about why and when they gamble and to structure their time differently. Most of the study participants spend about $500 a month, but they often don't realize the extent of their gambling until they try to count it all up. Interestingly, just participating in our study generally helps them gamble less."

Dr. Petry's research so far indicates that even a brief intervention can help make gamblers more aware of how much money they spend on lottery tickets, sports wagers, and slot machines over the course of a year. Participants in the ongoing study are split 60-40 male to female, are usually in their mid-forties, and are generally well-educated. About two to five percent of people in the general population suffer from a gambling problem at some point over the course of their lifetime.

Giving Up the Wheel

2001
Richard Marottoli, M.D., M.P.H.

Just like Miss Daisy of movie fame, many of us at some point may have to face the fact that it's time to give up driving.

"While we all tend to slow down somewhat as we get older, if there's substantial cognitive decline, vision loss, or impaired physical ability, driving safety may be affected," says geriatrician Richard Marottoli, M.D., M.P.H., associate professor of internal medicine at Yale University School of Medicine and director of Geriatrics and Extended Care at the Veterans Administration Hospital in West Haven. "Though most people adjust appropriately to changes as they age and remain safe drivers, clinicians need tools that can help them assess potential dangers and intervene before an accident happens."

He has the difficult job of helping families tell mom or dad it's time to surrender the car keys. "Most people who need to stop driving come to the decision on their own," Dr. Marottoli says. Losing the independence of one's own car has such a huge impact on someone's life that medical expertise can sometimes help soften the blow when telling someone that they must curtail or give up driving completely. Adult children are often closely involved in assessing their parents' fitness for driving. Answers to a number of questions may help in this process. Do the drivers have substantial visual deficits or hearing impairments? Have they sensibly compensated for poor night vision by limiting or giving up driving after dark? How is their cognitive function and mental clarity? Have they had car accidents or near misses?

In general, doctors do not like to be placed in the role of police, says Dr. Marottoli, who has developed quantitative tools and questionnaires to help evaluate older drivers in a variety of settings. Using such tools and questionnaires can help provide evidence that makes the clinician, family, and driver feel more comfortable about what is often a difficult decision regarding whether to limit or stop driving. While these tools and questionnaires are designed to be used by any clinician, they may be helpful in certain circumstances for primary care physicians—whose practices may be filled with elderly patients and who don't want to become known as doctors who revoke licenses or to place themselves in a more adversarial relationship with their patients—to refer patients to a geriatrician to help make the determination.

Dr. Marottoli, who grew up in a close-knit, multigenerational Italian family, loves history, antique automobiles and archaeology. He knows the decision to relinquish the road can make someone's world much smaller, and sadder. "Patients, families, and health care providers need to identify ways to minimize the potential negative effects on their lifestyle," says Dr. Marottoli. "We need to work together and be creative about filling the vacuum giving up driving leaves behind."

Richard Marottoli, M.D., M.P.H., associate professor of internal medicine at Yale School of Medicine, helps assess driving ability in the elderly. In his work with outpatients at Yale-New Haven Hospital's Adler Clinic and the V.A. Hospital, Dr. Marottoli may wind up recommending that someone give up driving.

2001
Carol Pilbeam, Ph.D., M.D.

Skeleton Crew: Lab Tries to Rebuild Bone

Carol Pilbeam, Ph.D., M.D., a geriatrician and associate professor of internal medicine at the University of Connecticut Health Center, is studying apoptosis (programmed cell death) in the endlessly recurring process of bone formation.

You don't feel your bones weakening as osteoporosis destroys them. Vertebrae may fracture, shortening your stature and curving your spine. Silently and without warning, fragile bones break.

Each year in the United States, osteoporosis leads to 1.5 million fractures of the hip, spine, and wrist. Hip fractures are deadlier than most people realize. Up to 20 percent of hip fracture patients die within a year after the break and a quarter need long-term nursing home care. Although hip fractures occur twice as often in women, each year 80,000 men suffer a hip fracture and one-third die within a year from complications.

Why do we lose bone? Bone is constantly being renewed or "turned over," beginning with bone *resorption*, or bone breakdown, and ending with bone formation. The cells that resorb bone and form bone are derived by a process of differentiation and replication from stem cells in the bone marrow. Their lifetime is limited by *apoptosis* (programmed cell death). Bone turnover is an endlessly recurring cycle.

"All of our current drugs can decrease bone resorption, but these drugs make little new bone to replace all the bone that has already been lost," says Carol Pilbeam, Ph.D., M.D., a geriatrician at the University of Connecticut Health Center. "Moreover, many of these drugs have effects on parts of the body other than bone. One new treatment, intermittent parathyroid hormone, does appear to make new bone, but requires daily injections and is very expensive."

Imagine repairing fractures with medications that target broken bones. "If we can develop drugs that enhance or replace stem cells in the bone marrow, we can potentially grow new bone," says Dr. Pilbeam. "I'm studying the life and death of *osteoblasts*, or bone-forming cells, to learn how bone grows and dies." One focus of Dr. Pilbeam's research is how the anti-inflammatory drugs that selectively inhibit the activity of COX-2 enzymes—marketed under the tradenames Vioxx™ and Celebrex™—affect bones. Widely prescribed for chronic joint pain, rheumatoid arthritis or even cancer, these drugs need further study for their effect on bone formation.

After earning her Ph.D. in geology, Dr. Pilbeam worked as a geophysicist, but grew tired of analyzing heat flow data from the moon and enrolled in medical school at Yale University at the age of 36. An associate professor of internal medicine at UConn as well as a geriatrician, she plasters her office door with photos of her airedale terrier, Raleigh, and is passionate about her work with the elderly. "My work is meaningless without patients, but research funds are hard to come by for clinician scientists. The Donaghue funding has meant a great deal to me, allowing me to try out new avenues of research that would otherwise have been impossible."

RNA Editing Beyond the Genome

2001
Robert Reenan, Ph.D.

What happens when a fruit fly gets the symptoms of Alzheimer's disease? Although *Drosophila* in the wild don't get Alzheimer's, Robert Reenan, Ph.D., associate professor of genetics and developmental biology at the University of Connecticut Health Center, has figured out a way to mimic the neurological deterioration of the devastating human disease.

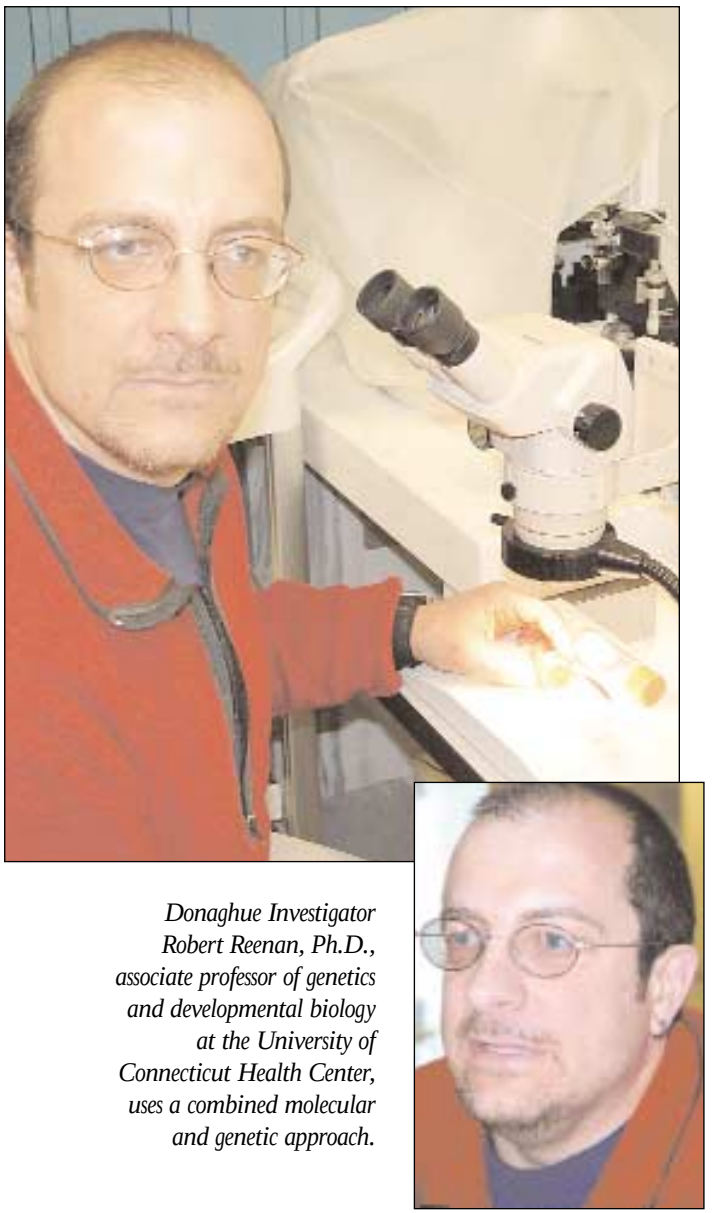
As a Donaghue Investigator, he is elucidating the molecular mechanisms that underlie electrical signalling in the *Drosophila* nervous system through a combined molecular and genetic approach. *Drosophila* conditional behavioral mutants such as those affecting ion channels are useful in identifying components of the electrical signalling apparatus.

Pre-mRNA editing by enzymes called *adenosine deaminases acting on RNA* (ADARs) appears to have played an ancient and primary role in the evolution of nervous system function and behavior. RNA editing fosters protein diversity and is involved in signalling components of the nervous system. "We used to think that information transfer occurred in a linear way from DNA to RNA to protein synthesis," explains Dr. Reenan. "Now we know that RNA editing chemically modifies the messages coded by the genome. This discovery has a profound effect in understanding how electrical signalling affects ion channel and receptor function in the brain."

He has figured out a way to induce a mutation called dADAR by "knocking out" a specific gene in the fly. These dADAR mutants are severely compromised neurologically as adults, suffering tremors and seizures. "If we provide 'nursing home' conditions for neurologically compromised flies, we can keep them alive, but their locomotor coordination is abysmal," says Dr. Reenan, who adds that dADAR mutants can be *rescued* with an enzyme that restores much of their normal neurological function. "It's amazing—within 10 days mutant flies are walking and flying as though you'd flipped a switch."

It's almost unheard of to go directly from *Drosophila* to humans, explains Dr. Reenan, who is investigating a gene in the brain and spinal cord that is shared by both fruit flies and people. "It goes to show that just having the genome of a species is not enough. We don't know to what extent human diseases are RNA editing disorders."

The RNA editing process, which he has found so far in four different regions, appears to be ideal for fine-tuning or modifying behavior in the nervous system. "We think we have the information for a significant breakthrough," says Dr. Reenan, a dedicated mountain biker who races throughout New England. "I am so passionate about my lab that I do a lot of benchwork myself. I like using my own hands."



Donaghue Investigator Robert Reenan, Ph.D., associate professor of genetics and developmental biology at the University of Connecticut Health Center, uses a combined molecular and genetic approach.

2002
Elizabeth Bradley, Ph.D.

Process Improvement in Hospitals

Dr. Bradley, director of the health management program in the Division of Health Policy and Administration at Yale's School of Epidemiology and Public Health, is investigating use of beta-blockers after AMI and how hospitals can translate research into practice.

Cardiovascular disease is the leading cause of death in the United States. The scientific evidence that beta-blocker use after a heart attack reduces subsequent cardiac events—and mortality—is substantial and convincing. So why do hospitals vary in the time between arrival and treatment in the emergency room for a heart attack, more accurately termed an *acute myocardial infarction* (AMI)? Why don't all hospitals give beta blockers and other medications at discharge, including aspirin, for AMI?

Elizabeth Bradley, Ph.D., associate professor in the Department of Epidemiology and Public Health at the Yale School of Medicine and director of the health management program in the Division of Health Policy and Administration, is studying the reasons for such variations across hospitals. Her most recent study, focusing on the care of patients with heart attacks, found that administrators differed in their communication with clinicians, their commitment to allocating resources to improve care, and their advocacy for improvement efforts."Managers, it seems, can create the context for positive changes in clinical care," she says.

Dr. Bradley's research as a Donaghue Investigator aims to identify "best practices" in successful hospitals in an effort to help heart attack patients in Connecticut and around the country. The culture of a hospital, as fostered by the hospital managers, may play a more important role than previously realized in sustaining and promoting high-quality care, she says. "Management is an underappreciated key element in quality improvement."

Working with experts in cardiology, organizational behavior, and statistics, she is seeking to evaluate the effectiveness of total quality management efforts in hospitals. If hospitals can implement process improvement strategies effectively, it will be of enormous "practical benefit" for patients, but "organizational change often required for real improvement takes time," says Dr. Bradley, a former hospital administrator at Massachusetts General Hospital in Boston. "Clinical and administrative leadership are critical."

Married and the mother of three children ranging in age from four to 10 years old, Dr. Bradley conducts a women's a cappella choral group in Wallingford. Her office walls are papered with her children's artwork, lending a bright and inviting warmth to the space.

Her first task is to identify the strategies that are most effective in improving processes of care for patients with heart attacks, particularly among hospitals in Connecticut, and then to disseminate her findings locally and nationally. "We often know from research what interventions work well for treating AMI," says Dr. Bradley. "The challenge is to put them into practice."

Proteomics and Pharmaceutics

2002
Kevin Claffey, Ph.D.

Every three minutes a woman is diagnosed with breast cancer and every 12 minutes another woman dies. Fewer than a third of the women who develop the disease have any identifiable risk factors, and less than five percent have a family history of a "breast cancer gene." Yet the average American woman has a one-in-eight chance of developing breast cancer during her lifetime.

"Right now, all breast cancer patients fall into generalized treatment groups," says Kevin P. Claffey, Ph.D., assistant professor of physiology at the Center for Vascular Biology at the University of Connecticut Health Center. "We know that they're not all the same—and quantitative diagnostics can help differentiate patients as to their disease type and apply select therapeutics specific to each individual."

The new science of *proteomics*—the study of proteins within cells—is driving pioneering research into targeted pharmaceutics. "Proteomics will someday allow development of drugs designed to target specific molecules at the cellular level," says Dr. Claffey. "Our goal is to translate basic research into treating individuals in a more effective, mechanistic manner."

A tumor mass only a centimeter in diameter can contain as many as a billion cells. How can doctors prevent their spread elsewhere in the body? Metastasis, with its far-flung colonies of invading cells gone awry, kills most of cancer's victims. By unleashing proteases—enzymes that chew up tissue around the tumor—cancers grow and spread.

Dr. Claffey's lab is studying the response of tumor cells to hypoxic stress and activation of signal transduction cascades, profiling invasive proteins and those involved in signalling pathways targeted by drug therapies. Will proteomics, now in its infancy, shape the chemotherapy of the future? Will patients someday be screened for tumor suppressor genes, errant proteins or growth factor receptors? "We treat patients with high-dose radiation and chemotherapy, but do we know how this affects cancer cells that survive the treatment?" asks Dr. Claffey. "Radiation and tamoxifen-resistant clones are very much worse than the original cancers."

The Donaghue Investigator program rewards innovative thinkers in ways other funders can't, asserts Dr. Claffey. Along with additional funding from the National Cancer Institute (NCI) and the National Institutes of Health, the Donaghue grant is giving him the freedom to explore alternate paths. "Someday, I think doctors will use proteomics to do molecular profiling for each individual patient," says Dr. Claffey. "Biomarkers will allow us to detect small amounts of tumor before the disease spreads. Eventually, it will change the way we treat breast cancer."

Tumor tissue microarrays useful in confirming changes being studied by Kevin Claffey, Ph.D., will come from David Rimm, M.D., Ph.D., a 1998 Donaghue Investigator who is a molecular biologist and associate professor of pathology at Yale School of Medicine.

2002
Barbara Kazmierczak, M.D., Ph.D.

The Best Defense is A Good Offense

Donaghue Investigator Barbara Kazmierczak, M.D., Ph.D., assistant professor of internal medicine at Yale School of Medicine, is investigating how epithelial cells that line the respiratory and gastrointestinal tracts signal the healthy immune system to fight pathogens.

Bacteria that lurk harmlessly in soil and water can be lethal in a hospital. Opportunistic lower respiratory tract infections caused by bacterial and fungal pathogens often sicken and kill patients with compromised immune systems. How do healthy lungs defend against microbial pathogens?

With her Donaghue grant, Barbara Kazmierczak, M.D., Ph.D., assistant professor of internal medicine at Yale School of Medicine, is investigating how epithelial cells that line the respiratory and gastrointestinal tracts signal the healthy immune system to repel attackers. When the body's natural defenses fail, disease-causing bacteria can be deadly.

"*Pseudomonas aeruginosa* is a virulent disease-causing bacteria that can do a lot of damage to the lungs of people on ventilators," says Dr. Kazmierczak. "It also infects burn victims and patients with cystic fibrosis. It's so resistant to antibiotics that it's been found growing in bactericidal soap." Pseudomonas can lead to ventilator-associated pneumonia or infect catheterized patients.

The bacteria exploit pre-existing epithelial damage to cause acute infections of the cornea, skin, lower respiratory tract, and urinary tract. "We're studying how epithelial cells help trigger the innate immune response to pathogens," she says. "This 'first-response' to infections may be particularly important in patients whose immune systems are otherwise compromised by medications taken after organ transplants or during cancer chemotherapy."

One of her goals is to develop a rapid diagnostic test that will allow physicians to assess how virulent—and how likely to cause serious infection—any particular Pseudomonas isolate is before beginning treatment. "A lot of cystic fibrosis patients are colonized with Pseudomonas as small children, and by the time they reach their thirties they usually harbor a number of mutated and resistant strains. Since resistance develops as a consequence of antibiotic use—and misuse—any strategy that allows us to limit the use of antibiotics to situations where they're really necessary can delay the emergence of such resistant and difficult-to-treat strains."

Biotech companies are devising new classes of experimental pharmaceutics to repulse invading pathogens. A current emphasis in Dr. Kazmierczak's lab is understanding how bacteria turn on the production and secretion of proteins that can affect the behavior of human cells, and how such pathways might be disrupted by new classes of antimicrobials.

Dr. Kazmierczak recently moved to Connecticut from San Francisco with her husband, a French scientist who works with a biotech firm that develops commercial applications from research. "In another life, I would have been a concert pianist," she says, "but science has always been my passion."

The Donaghue Foundation

The Patrick and Catherine Weldon Donaghue Medical Research Foundation is a charitable trust created pursuant to the will of Ethel F. Donaghue, late of West Hartford, Connecticut. The Foundation, which began operations in 1991, is governed by Fleet National Bank and Raymond S. Andrews, Jr., Trustees. The Foundation is exempt from income tax under Section 501(c)(3) of the Internal Revenue Code of 1986, is a private foundation within the meaning of Code Section 509(a), and is subject to the jurisdiction of the Probate Court for the District of West Hartford.

The Foundation's Purpose

The Foundation established hereunder is created and shall be operated solely for the purpose of providing financial assistance for research in the fields of cancer and heart disease and/or other medical research to promote medical knowledge which will be of practical benefit to the preservation, maintenance and improvement of human life.

From the Will of Ethel F. Donaghue (1896–1989)

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