2003 Annual Report

BURROUGHS
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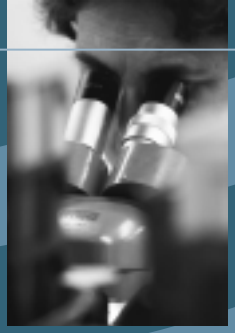

The Burroughs Wellcome Fund

is an independent private foundation

dedicated to advancing the biomedical sciences

by supporting research and other

scientific and educational

activities.

Depicted in BWF's logo, the eye of the
ancient Egyptian god Horus is considered a symbol of health.

2003 Annual Report

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Contents

About the Burroughs Wellcome Fund

The Burroughs Wellcome Fund is an independent private foundation dedicated to advancing the biomedical sciences by supporting research and other scientific and educational activities.

Within this broad mission, we seek to accomplish two primary goals—to help scientists early in their careers develop as independent investigators, and to advance fields in the basic biomedical sciences that are undervalued or in need of particular encouragement.

BWF has an endowment of about $600 million, and we award approximately $25 million in grants annually in the United States and Canada. We channel our financial support primarily through competitive peer-reviewed award programs, which encompass five major categories—basic biomedical sciences, infectious diseases, interfaces in science, translational research, and science education. BWF makes grants primarily to degree-granting institutions on behalf of individual researchers, who must be nominated by their institutions. To complement these competitive award programs, we also make grants to nonprofit organizations conducting activities intended to improve the general environment for science.

The Burroughs Wellcome Fund was founded in 1955 as the corporate foundation of Burroughs Wellcome Co., the U.S. branch of the Wellcome pharmaceutical enterprise, based in the United Kingdom. The Wellcome enterprise was started in 1880 by two young American pharmacists, Henry Wellcome and Silas Burroughs, who had moved to London to manufacture and sell "compressed medicines"—that is, pills—which the pair believed could replace the potions and powders of the day.

Their firm prospered. After Silas Burroughs died in 1895, Henry Wellcome directed the growth of the company into an international network with subsidiaries in numerous countries on several continents. As the business grew, Henry Wellcome held firm to his strong belief that research was fundamental to the development of excellent pharmaceutical products—a belief he put into practice by establishing the industry's first research laboratories.

When Henry Wellcome died in 1936, his will vested all of the corporate shares in a new organization—the Wellcome Trust—devoted to supporting research in medicine and allied sciences and to maintaining museums and libraries dedicated to these fields. Over the decades, the Trust grew to become the world's largest charitable foundation devoted exclusively to the biomedical sciences.

In 1955, leaders at the Wellcome Trust and Burroughs Wellcome Co.-USA envisioned an extension of this effort in the United States—and so was born the Burroughs Wellcome Fund. After nearly four decades as a corporate foundation, BWF in 1993 received from the Trust a $400 million gift that enabled us to become a foundation fully independent of the Wellcome Trust and the Burroughs Wellcome Co. Though we are today an independent philanthropy, our history and joint program activities allow us to maintain productive ties with the Wellcome Trust.

With this increase in assets resulting from the Wellcome Trust endowment, BWF has been able to play a larger role in funding biomedical research, including extending our support into Canada. In carrying out this work, BWF is governed by a Board of Directors composed of distinguished scientists and business leaders, and our competitive award programs are guided by advisory committees composed of leading researchers and educators.

The importance of curiosity-driven research, as endorsed by Henry Wellcome, continues to be our guide. Thus, more than a century after two enterprising American pharmacists set in motion their pioneering partnership, the Burroughs Wellcome Fund remains committed to the belief that fostering research by the best and brightest scientists offers the fullest promise for improving human health.

President's Message

"Geniuses are ferments; and when they come together, as they have done in certain lands at certain times, the whole population seems to share in the higher energy which they awaken. The effects are incalculable and often not easy to trace in detail, but they are pervasive and momentous."

—William James, 1842-1910

"The most critical and longest-term investment in the research system is the development of career scientists who contribute to the long-term success of the enterprise through both their own research efforts and their training of future generations of scientists."

—(Institute of Medicine, 1990)

These quotes underscore the Burroughs Wellcome Fund's strategy—crafted by our Board of Directors—to invest in the career development of scientists early in their careers and to support investigators in undervalued or underfunded areas of science. The Fund's mission is to advance the biomedical sciences through the support of research and education. For that reason, the Fund is deeply concerned about the health of the national research enterprise. What should a successful and vibrant research environment encompass? We believe a positive environment for the biomedical sciences should:

- Identify and encourage talented individuals to pursue health research careers
- Provide stable research support for talented scientists throughout their careers
- Offer flexibility in allocating resources to foster creativity and meet changing demands
- Provide adequate modern laboratories and equipment necessary for scientific research and training

As a fund, we are too small to take on all the components of a healthy research enterprise. We are a niche funder mindful of the much larger investment the National Institutes of Health and industry make, so we have selected career development as our grantmaking flagship: we provide flexible, long-term support that enables young scientists to innovate and take risks. BWF makes grants in the United States and Canada. Both countries recognize that an appropriately trained and configured science and technology (S&T) workforce is essential to fostering economic growth and contributing to security issues now so compelling in the wake of September 11, 2001, and the war with Iraq.

Unfortunately, our sagging economy and the poor performance of the stock market have had a critical impact on the funding climate of the last three years, eroding BWF's ability to make additional grants. The financial downturn also forced us to cut the number of awards in each program. For the 2003-2004 cycle, BWF did not make awards in three programs—Interfaces, Translational, and Infectious Diseases—but will fund all three programs at previous levels in the 2004-2005 cycle, receiving applications in 2004.

Below, I will outline some of the trends in the S&T workforce, as well as gaps, and tell you what BWF is doing to address a few targeted S&T workforce needs.

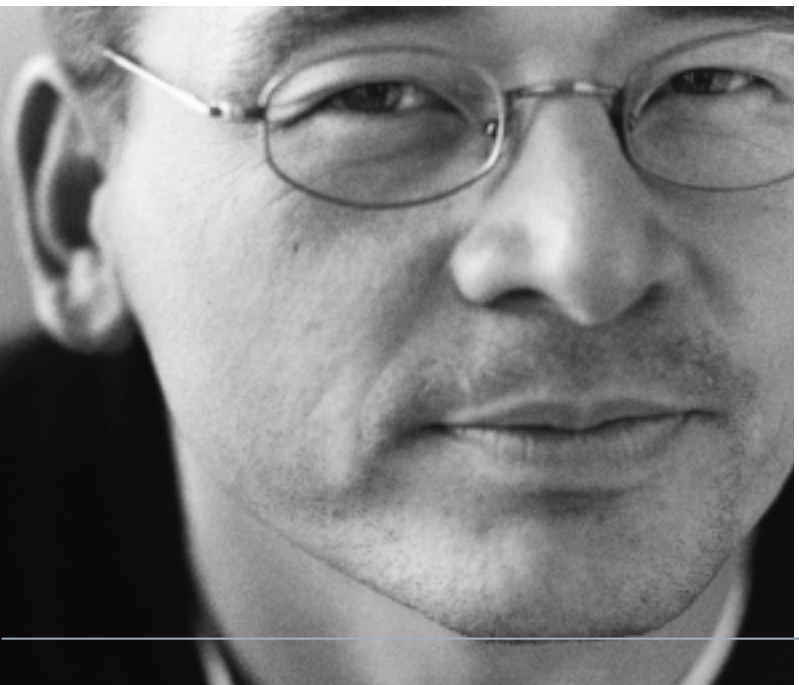
Status of the research workforce in the United States

Trends in the North American S&T workforce have included:

- An increasing number of foreign graduate students
- An increase in global competition for talented scientists
- A leaky pipeline that loses science-oriented students between high school and college graduation
- Continued underutilization of minorities (especially the underrepresentation of Hispanics and African Americans in the workforce)
- Increasing numbers of women in some fields but not in others

A 2002 publication of the National Science Board estimated that foreign-born scientists and engineers make up 27 percent of the S&T workforce. Remarkably, more than 50 percent of postdoctoral S&T students are foreign born; approximately 60 percent remain in the United States for their scientific careers. The United States benefits greatly from this foreign-born talent, although some worry that this influx of "cheap labor" has discouraged American students from selecting S&T careers. In a 1999 study (Levin, Sharon G. and Stephan, Paula E. 1999. "Are the Foreign Born a Source of Strength for U.S. Science?" *Science* 285 [August 20]: 12-13), researchers from the University of Missouri and Georgia State University found that foreign-born scientists have a disproportionately greater impact than their American counterparts as first authors of frequently cited papers and as founders or chairs of biotechnology companies. Additionally, they were more likely to be among the contributors of highly cited patents and members of the National Academy of Sciences.

Fallout from the September 11 terrorist attacks has led to various proposals to restrict the number of foreign-born students studying in the U.S. on temporary visas. This despite the fact that in the past 19 years, temporary, foreign-born residents have accounted for more than 50 percent of the rise in Ph.D.s in the U.S.



For foreign-born researchers, the post 9/11 hurdles to studying and working in the United States can mean that some wait as long as five months or more to enter the country when four to six weeks used to be standard.

The Office of Homeland Security also is looking at limiting researchers' access to data and methodologies. The issues at hand are complex and troubling The unintended consequences of restricting the free exchange of science could signal a serious setback for the national research enterprise, leading to fewer advances and discoveries and duplication of research results.

For foreign-born researchers, the new, post 9/11 hurdles to studying and working in the United States can be prohibitive. Anecdotal reports from universities and research institutions reveal that some foreign students are waiting as long as five months or more to enter the United States, when four to six weeks used to be standard. There are also reports of eminent scholars who cannot get into the country and research projects halted because the team is waiting for a foreign scholar to arrive. Institutions have to conduct more extensive background checks, which also can delay the process. The intention is to improve security, but the net result is that the new restrictions slow down research and discourage some of the best minds from contributing to the U.S. research enterprise.

In addition, the globalization of the research labor force means that the United States and Canada will face more competition for researchers from other parts of the world. For example, China has opened seven new postdoctoral research centers in its central Henan Province. So far, at least 140 research centers have been established in China, where approximately 7,000 postdoctoral researchers are working in 12 disciplines, and postdoctoral researchers in China are predicted to top 12,000 by 2005 (Xinhua News Agency, 14 April, 2002). In addition to Japan and Europe's major economies, Scandinavian countries have emerged as innovative centers, as have Singapore, Taiwan, South Korea, Ireland, and Israel. These countries are ratcheting up their ability to educate and use scientific and technological talent.

While the United States faces more competition abroad for students and is erecting more barriers to their entry at home, at the same time, the pipeline carrying our own students into science is failing to bring us enough well-educated young people. The students who finish college as science majors do not reflect the population demographics, and their numbers are nowhere near what we need for the future, especially if we can no longer draw as deeply from the foreign talent pool.

For foreign-born students, the benefits of a career in the U. S. may outweigh the costs, but the best and brightest U.S. and Canadian students may well choose to pursue careers in law and medicine over science and technology if conditions do not improve.

National Science Board data indicate that the number of undergraduate U.S. students in engineering and the physical sciences has dropped below the numbers reached in the early 1990s. As science, mathematics, engineering, and technology degrees are decreasing in the United States, the U.S. Bureau of Labor Statistics predicts a 51 percent increase in these jobs between 1998 and 2008. How will we fill those jobs?

If the United States and Canada must look for their future workforces increasingly within their own populations, today's workforce of scientists and engineers no longer mirrors either country's population. According to the latest statistics from the National Science Foundation, the S&T workforce in the United States is approximately 27 percent female, 11 percent Asian, 3.5 percent African American, and 3.4 percent Hispanic. In the biological sciences, however, women comprise 42 percent of the workforce. Engineering attracts the fewest women—only 9.5 percent. Taken together, women and underrepresented groups make up half to two-thirds of the U.S. population and comprise the nation's new majority. To assure its future, the research enterprise must tap this pool of talent. But in order to attract and retain such students, careers in science must provide adequate salary, reasonable career tracks, and quality of life for those who enter. Academia, the wellspring of this talent pool, must especially consider its role as an employer and the composition and status of scientists it trains.

Issues facing young scientists

For those with the interest, talent, and tenacity to pursue Ph.D.s in the sciences, the road can be bumpy. In the biosciences, aspiring professionals put in an average of 10-12 years of study after their baccalaureate. The Ph.D. program can take seven to eight years, followed by two to five years of postdoctoral work. The path of physician-scientists takes even longer as requirements to gain clinical competency are added to gaining research experience. Lengthy preparation time means that most young researchers are in their early 30s before they embark on their professional careers. If they want faculty positions, they may not be eligible for tenure until their late 30s at the earliest. During this extended training period, the pay is low (with a median of $35,000 annually), the hours are long, and this comes at a time when young scientists are marrying and having families. In addition, there are still many institutions that don't provide retirement or other benefits because postdoctoral fellows technically are neither students nor full-time staff.

In addition, competition for faculty positions, research support, and grants is keen. Since 1980, the percentage of NIH biomedical grants awarded to researchers aged 35 and under has plunged from 23 percent to 4 percent, while the number given to investigators over 46 years of age has increased sharply. This doesn't mean that young faculty are not competing well for grants. Rather, it is an indicator of the decline in the relative number of young professors in the system and the aging of the professoriat. Limited resources promote a tournament model of competition where researchers have the opportunity to win big prizes—tenure, a large grant, a named chair, scientific fame—based on differences in achievement that may be marginal. The tournament model puts excessive pressure on investigators, because the slightest edge can make the difference between success and failure. For foreign-born students, the benefits of a career in the United States may outweigh the costs, but the best and brightest U.S. and Canadian students may well choose to pursue careers in law and medicine over S&T if conditions do not improve. Fortunately, policymakers are beginning to recommend ways to improve the system. In a project approved by the National Research Council, the Committee on Science, Engineering, and Public Policy (COSEPUP) published a guide for institutions and individuals involved in the postdoctoral experience. The book, titled *Enhancing the Postdoctoral Experience for Scientists and Engineers*, recommends a number of guidelines for academic institutions, advisers, and funding organizations to make life better for postdoctoral fellows. Professional societies also have taken up the postdoctoral cause, and funders such as the Sloan Foundation are bankrolling science master's-degree programs that can shorten training time and fill a number of workforce gaps.

Trends in science: BWF's role in addressing workforce gaps

BWF core programs—basic biomedical sciences, interfaces in science, translational research, infectious diseases, and science education—are all structured to address selected workforce needs in light of the new trends in science. You will learn more about these programs in the pages that follow.

Recent advances in biomedical research, such as mapping the human genome as well as the sequencing of more than 100 other organisms, provide researchers the means to delve more deeply into molecular biology than ever before. Consequently, there is a growing trend toward mathematization of biology, comparative genomics, proteonomics, interdisciplinary science, systems biology, and adapting technology for specific uses in the lab. Mathematicians, physicists, computer scientists, engineers, and biologists will increasingly work across disciplines to tackle complex biological questions and pull together information from disparate sources. Our Interfaces in Science program brings together the physical and biological sciences and began as a program to support "experimental" institutional training programs that created prototypes for a new kind of graduate and postdoctoral training. More recently, like our signature program in the basic biomedical sciences, the Interfaces program is now providing career awards to scientists well trained in the physical and quantitative sciences who wish to work on important biological questions. The long-term, flexible support provided by these awards is intended to enable risk-taking and innovation while providing bridging support between the end of the postdoctoral period and beginning faculty status. A paper by Drs. Georgine Pion and Martin Ionescu-Pioggia, "Bridging Postdoctoral Training and a Faculty Position: Initial Outcomes of the Burroughs Wellcome Fund's Career Awards in the Biomedical Sciences" (*Academic Medicine*. 2003.78:2), provides evidence of the success of this funding approach.

BWF has had a long-standing interest in infectious diseases, supporting the development of molecular parasitology, molecular pathogenic mycology, and malaria initiatives. In collaboration with the Wellcome Trust, BWF has funded research aimed at the developing world. More recently, our interests have focused on the host/pathogen relationship—a more systemic view of infectious disease. Many sciences beyond microbiology need to help develop a new understanding of the host/pathogen interface, including immunology, ecology, evolution and plant pathology, as well as the computational sciences, which, as noted above, can begin to harness the quantities of new data and help pose new hypotheses. The March Banbury Conference (manuscript under preparation), developed in collaboration with the Ellison Foundation, illuminated some of the funding and collaborative initiatives that can advance knowledge across different microbiological systems and in collaboration with other sciences. Dr. Victoria McGovern, our program officer in infectious diseases, made a presentation on workforce needs in infectious diseases at an Institute of Medicine Emerging Infections Forum in June.

One of the most critical challenges facing the research enterprise is translating new discoveries quickly from bench to bedside so that they can benefit patients. BWF Program Officer Dr. Nancy Sung addressed this issue as lead author of an article—"Central Challenges Facing the National Clinical Research Enterprise"—published in the March 12, 2003, issue of the *Journal of the American Medical Association*.

The article notes that there are four major challenges in surmounting two translational blocks: a growing need for research study participants; the need for more comprehensive information technology; funding; and, most importantly for our purposes here, a shortage of adequately trained clinical investigators. Many leading physician-scientists, including Drs. Wyngaarden (Wyngaarden, James B. 1979. "The Clinical Investigator as an Endangered Species." *The New England Journal of Medicine*. 301 [December 6]: 1254-1259), Nathan (Nathan, David G. 1998. "Clinical Research : Perceptions, Reality, and Proposed Solutions." *The Journal of the American Medical Association*. 280 [October 28]: 1427-1431), and most recently Rosenberg (Rosenberg, Leon E. 1999. "The Physician-Scientist: an Essential—and Fragile—Link in the Medical Research Chain." *Journal of Clinical Investigation*. 103 [June]: 1621-1626), have noted the dearth of physician-scientists. BWF programs in the biomedical sciences and our Clinical Scientists in Translational Research, both provide awards to physician-scientists. The translational program is aimed at late-assistant and early-associate professors to buy their time from clinical service for research and to support their roles as mentors of the next generation of researchers.

One of the biggest challenges facing the nation is how to create a better pipeline into the sciences, especially for under-represented minorities and women.

The challenge begins with K-12 education and the kind of teaching that will attract more student enthusiasm for studying science, mathematics, and technology. Federal data indicate that only 17 percent of U.S. high school seniors are proficient in the sciences, a number below that of students in other industrialized countries.

In North Carolina, BWF is addressing the pipeline issue through two initiatives. One is our ongoing Student Science Enrichment Program (SSEP), which makes awards to nonprofit organizations serving North Carolina middle- and high school

students. The SSEP awards support programs that provide creative science enrichment activities for promising students and specifically target programs that recruit heavily in under-represented groups. Since the SSEP's inception in 1996, BWF has awarded more than $8 million to support 61 awards at 39 organizations across North Carolina. To date, SSEP has reached more than 23,000 students (65 percent minority; 62 percent economically disadvantaged; 65 percent rural; 41 percent female; and 50 percent gifted), nearly half of whom, after completing the program, report that they view science as a career option.

In conjunction with investing in the SSEP program, BWF also has been busy building the state's capacity to improve pre K-12 science, mathematics, and technology education by making grants to a number of organizations. These organizations include the Public School Forum of North Carolina, which provides legislators, state Board of Education members, and the media with research-based data and policy information on K-12 education, and the Grassroots Science Museum Collaborative, which enables more than 21 North Carolina science museums and aquariums to collaborate in program development. Carr Thompson, our education program officer, has been working with national organizations such as the National Sciences Resource Center and the American Association for the Advancement of Science to disseminate the BWF approach and to share the evaluation of our program more widely.

Most recently, BWF has embarked on an exciting journey to create the new North Carolina Science, Mathematics, and Technology Education Center (SMT Center), whose mission is to improve pre K-12 student performance in SMT. We were fortunate to have recruited longtime educator Dr. Sam Houston to lead this effort. Dr. Houston has been a teacher, a principal, an adjunct professor of education, a school superintendent, and a consultant on education. He also worked for five years as executive director of the North Carolina Education Standards and Accountability Commission and was executive director of the University of North Carolina Center for School Leadership Development. He was named North Carolina Outstanding Community Educator in 1992 and was recognized by the RJR-Nabisco Foundation in 1993 as a leader in implementing education and preparing American students for the 21st century.

Our board believes that the best use of our dollars is to invest in human capital—expert and superb scientists who will support the research enterprise's capacity to foster both economic growth and technological advances that will improve human health.

You will learn more about all our programs in the material that follows.

The Career Awards in the Basic Biomedical Sciences (CABS) program, now in its ninth consecutive year, added 13 new investigators to the program's existing cadre of 166 scientists.

The latest awardees include six women and five physician-scientists with research topics spanning basic mechanisms that regulate memory to immunity against tuberculosis. To date, this program has approved approximately $85 million in awards and represents BWF's single largest long-term investment in advancing the careers of young scientists in the United States and Canada. We receive an average of 175 applications annually, reflecting a highly competitive award rate that varies from 9 to 13 percent, depending on the number of awards offered. The consistent number of applications to this program over time is a strong indicator of the continuing need for postdoctoral-faculty bridging programs in the current scientific economy.

Since the program began, the BWF Board of Directors has supported the practice of monitoring program outcomes as a way of gauging the success of their investment. To monitor the progress of the program, BWF surveys CABS recipients annually on a set of critical outcome variables. To our knowledge, we are one of the few foundations with a comprehensive ongoing outcome evaluation program. This year Pion and Ionescu-Pioggia published an article summarizing program outcomes for the 101 grant recipients who received awards during the first five years of the program (*Academic Medicine*. 2003.78:2). Of those surveyed, 77 percent of eligible postdocs had obtained tenure-track faculty positions in research-intensive institutions combined with significant university funding to start laboratories; 78 percent had built research programs that attracted external support; and 95 percent credited the award with facilitating their search for faculty jobs. As importantly, most CABS recipients thought the award made it possible for them to pursue research ideas that might have been considered risky or premature by other funders. Since the article was written, 100 percent of eligible awardees have achieved faculty status.

Although BWF needs to conduct long-term follow-up to determine the ultimate value of early career funding, these preliminary results strongly suggest that BWF's dollars have been well spent in terms of helping talented, advanced post-doctoral fellows bridge the postdoctoral years and the faculty position and become independent scientific investigators. To further assess the value of early career funding, BWF is undertaking a study comparing outcomes for applicants who received funding under CABS and those who did not.

Many factors contribute to the success of the CABS program, including the flexibility of our awards, our promoting networking opportunities between our grant recipients and the larger community of science, and especially, providing our awardees with career development training. Last year, BWF and the Howard Hughes Medical Institute (HHMI) codeveloped and offered a comprehensive three-day course in laboratory management skills to 130 awardees from both organizations. The goal of the course was to provide new faculty with all the skills they need to manage a laboratory at a time when their attention is directed at adjusting to the research, administrative, and clinical demands of the first faculty position, and obtaining ongoing research funding. We believe this course will help jump-start award recipients' research programs and is a form of career insurance on the investments we have made in their research. At the annual American Association of Medical Colleges' Graduate Research and Education Training (GREAT) meeting in April, we made a poster presentation summarizing the course, which was met with considerable interest.

This year BWF and HHMI have focused on turning the 14 sessions included in the course into a publication that will serve as a reference guide in laboratory management. The guide is accessible on the Internet at **www.hhmi.org** and free print copies are available to postdoctoral organizations and policy-makers nationwide. We hope that postdoctoral organizations, professional societies, universities, and other funders will use the guide to develop much needed laboratory management courses for their own constituencies across the nation. In 2005, BWF and HHMI plan to revise the course and offer it again to our grant recipients.

Dr. Matt Redinbo: PXR* and Promiscuous Enzymes

At this point in his career, Matt Redinbo might have been teaching Beowulf instead of biochemistry and writing a critique of John Steinbeck rather than a scientific paper on the crystal structure of human carboxylesterase 1. After his undergraduate work in biochemistry and English, the young researcher had to make a tough choice: whether to pursue a Ph.D. in English literature or go on with biochemistry. Already accepted as a biochemistry graduate student at the University of California—Los Angeles, Dr. Redinbo remembers talking to English professors for some advice about his dilemma. "The English professors recommended that I go into biochemistry," says Dr. Redinbo, grinning. "They said at least I'd get paid as a postdoc rather than trying to live on a teaching assistantship."

Frequently, says Dr. Matt Redinbo, less than 5 percent of cancer drugs actually makes it to the tumor; the other 95 percent can lead to toxicity and side effects such as hair loss and nausea. The goal of his research is to design drugs that are more potent with fewer side effects.

He took their advice, but says at first he was not all that enthused about biochemistry—until he took his first class in structural biology. "Then the lights came on," he recalls. "In structural biology, you use computers, mathematics, physics; you end up with a detailed picture of what you're studying."

Now, he has no doubt he made the right choice. With a BWF Career Award and three subsequent NIH grants, the assistant professor heads up a busy lab at the University of North Carolina at Chapel Hill with a staff of 15 doing research in structural biology. Holding a joint appointment in the Department of Chemistry and in the School of Medicine, he also teaches classes in structural biology methods and DNA biochemistry.

"I enjoy mentoring graduate students," he says, "because they come in without preconceived notions and can get excited about the science, and their enthusiasm feeds yours." There's no lack of enthusiasm in Dr. Redinbo's demeanor as he talks about his research and what the BWF award has meant to his work and career. "The first 13 papers from my independent lab were funded partly or completely from my Career Award," Dr. Redinbo says. "The Career Award has made it possible for me to pursue research I normally couldn't because it's risky."

Currently, Dr. Redinbo is juggling three related research projects in structural biology: how proteins manipulate human DNA to keep it stable; how the human body recognizes drugs (drug receptors); and how the body metabolizes drugs. His findings in the area of drug recognition belie the notion that there is a protein specific to each type of drug. In fact, Dr. Redinbo says, one specific nuclear receptor molecule recognizes a vast majority of drugs we take. This drug-patrol protein, called PXR, fingers everything from antibiotics to anticancer drugs to herbal supplements. Once PXR recognizes a drug, it signals the liver to metabolize and get rid of the foreign substance. PXR can bind to many types of drugs because it has large cavities —or pockets—that can expand and conform to the shape of different drug molecules.

Dr. Redinbo's research on metabolites focuses on the crucial step between drug recognition and its excretion by the liver. Enzymes triggered by PXR begin the process of breaking down the drug and can metabolize many different compounds in the liver. "Drug metabolizing enzymes have to be promiscuous," he says, "because they have to take on a lot of different drugs." Right now, he's looking at the enzyme that breaks down heroin and cocaine.

Dr. Redinbo's research has profound implications for drug efficacy. "For example," Dr. Redinbo says, "frequently less than five percent of cancer drugs actually makes it to the tumor; the other 95 percent can lead to toxicity and side effects such as hair loss and nausea." The goal of his research is to understand how to design a drug that can slip by the PXR gatekeeper. "Then we can deliver one-tenth of the dose and get it past the liver," Dr. Redinbo explains. Consequently, a smaller dose could be more potent with fewer side effects.

His interest in science started as early as the second grade, Dr. Redinbo recalls. "I remember being in the second grade and reading fourth- and fifth grade science textbooks," probably, he thinks, by borrowing those of his older brother, now a physicist. His father is a computer scientist, his mother a speech therapist, and his sister a lawyer. "It's handy having a lawyer in the family," he says with a grin. "I pay my sister to go over all my legal contracts."

Dr. Redinbo met his wife, Liz, a geneticist, during his postdoc in Seattle. When there is spare time, Dr. Redinbo likes to spend it with his wife and two small children. He makes a point of being home in the evenings and on weekends, though his laptop is close at hand and usually gets a workout. Because of his abiding interest in literature, Dr. Redinbo says he usually reads fiction. John Steinbeck's *Cannery Row* is his latest choice, though he says he and his wife have been reading *Harry Potter*. "She got me hooked on *Harry Potter*," he says. "So instead of fighting over the books, we read them aloud to each other."

*pregnane X receptor

Dr. Maria Schumacher and Proteins: Up Close and Personal

Maria Schumacher looks at life at the most fundamental level. "You could call me a minimalist," she says. "I'm interested in understanding cell growth and development from a structural level. What I specifically want to understand is how the proteins involved in transcribing DNA into the countless other proteins involved in cellular activity carry out their functions at the atomic level."

To piece together this atomic picture, Dr. Schumacher, a 1999 recipient of a Burroughs Wellcome Fund Career Award in the Biomedical Sciences and an assistant professor of biochemistry and molecular biology at Oregon Health and Science University, uses x-ray crystallography. The concept is simple; the execution complex.

Using biochemical and genetic tools, she first isolates and purifies crystals of a protein in question. She next bombards the crystals with x-rays, and then uses mathematical techniques to analyze the "diffraction patterns" that result as the x-rays are scattered by the electrons in the crystals. "What you get is a picture of the protein's electron density, and we then do further computer modeling to produce a more detailed 'snapshot' of the protein's three-dimensional atomic structure," Dr. Schumacher says. "By examining crystals obtained from different stages of the protein's operation in the cell, we can essentially get pictures of the protein in action. These images are often quite beautiful."

Dr. Maria Schumacher's work has answered the question of how a pathogen can develop multi-drug resistance when its proteins are able to bind several structurally different drugs at once.

The images also hold a wealth of information. "They really let us see at a structural level how the protein works," she says. "Proteins don't simply keep their same shape at every stage of their action. Rather, they continually change shapes, and these structural changes are crucial to their performance. The images we produce not only give us important information about some basic life processes. Knowing the atomic structures of the proteins also may let scientists begin to design really specific drugs to target these molecules in cases where their malfunction leads to disease."

Dr. Schumacher says she developed her interest in "the basic questions of life" as a child growing up on a farm in southern Washington. "This curiosity lead me into chemistry during my undergraduate years at Portland State University, and ultimately to my current university, where I got a Ph.D. in biochemistry in 1995 and then was a postdoctoral fellow until being appointed to the faculty in late 2002."

As part of her postdoctoral work, Dr. Schumacher concentrated on imaging a protein involved in genetic regulation in the pathogenic bacterium *Staphylococcus aureus*. Her findings may prove valuable in helping to design strategies for coping with an increasing health problem: the proliferation of pathogens that are resistant to numerous drugs. "We determined the atomic structure of a regulatory protein that enables the bacterium to resist multiple drugs," she says. "We also were able to work out precisely how this protein functions."

This work explained for the first time how a protein is able, from a structural standpoint, to bind several structurally different drugs at once. "It turns out that the protein we imaged operates in an unusual manner," Dr. Schumacher says. "Most proteins have specific 'binding pockets' that enable them to attach to only one type of molecule. But this protein has really expansive pockets—actually there are many pockets within one larger pocket—that enable binding to numerous chemical structures. This insight has helped to open up the field in terms of understanding multi-drug resistance, and people are now looking for more structures like this in other systems."

The path to practical application of these findings is still long, Dr. Schumacher cautions. "It is always a lot of work to move from basic research to medical applications," she says. "But at the same time, this process almost always must start with understanding at a very detailed level how something works."

Among her current projects as a new independent investigator, Dr. Schumacher is focusing on how the process of genetic transcription, the conversion of DNA into proteins, begins in the parasitic protozoan *Trichomonas vaginalis*. "This is an ancient organism, and the transcription process it uses is relatively simple," she says. "This feature, combined with some other technical issues, makes *T. vaginalis* an excellent model system for asking questions that would be almost impossible to ask in higher organisms."

Dr. Schumacher collaborates on this project with Dr. Patricia Johnson of the University of California at Los Angeles School of Medicine, who is a 1998 recipient of a BWF Scholar Award in Molecular Parasitology. "I do the crystallography, the structural work, and Dr. Johnson does the laboratory work to assess actual protein function," Dr. Schumacher says. "We've now worked out the structures of a key protein, called the initiator binding protein 39, or IBP39, that initiates the transcription of nearly all of the genes in the organisms. It's really interesting that this single protein is responsible for so much of how the organism carries out this basic function."

Further, the scientists have determined some of the intricate—and until now mysterious—details of just how IBP39 kicks off the transcription process. "We found that IBP39 'recruits' another protein, called RNA polymerase, and brings it to a specific site on the DNA," Dr. Schumacher says. "This is critical, because it is the RNA polymerase that actually carries out the transcription process that leads to making other proteins. All by itself, then, IBP39 brings RNA polymerase to the correct site and orients it in the correct manner so that it can start its job. That was exciting to see, since this protein appears to do all of the jobs in this protozoan that tens or hundreds or thousands of proteins might be required to do in higher organisms."

Building on this work, the two scientists have recently targeted proteins in some higher organisms that seem to operate in a manner similar to IBP39. "These proteins have been known for some time, but what we've done is to identify their structural region that might be similar to the region we study in our primitive organism," Dr. Schumacher says. "We're going to be continuing these studies, and we're hoping this will add to the knowledge base of how transcription works in higher organisms."

There also may be a therapeutic payoff. *T. vaginalis* can be transmitted sexually from person to person, and many people, mostly women, develop the disease. "There are good drugs to treat this disease, but there also is some evidence that the protozoan is starting to develop multi-drug resistance," Dr. Schumacher says. "This needs more study. But in any event, understanding protein structure in the organism may help to identify new targets to attack with new drugs."

Despite all the technical challenges, probing the innermost structure of proteins is perhaps the easiest part of Dr. Schumacher's day. "It has been challenging to move from being a postdoctoral fellow to an independent researcher," she says. "Scientists are trained to 'do science,' but then all of a sudden you have to be a laboratory manager as well. Plus there are the increased challenges of grant writing. All in all, it's been fun—but not always easy."

Dr. Schumacher credits her BWF award with helping in the transition process. "I was able to develop projects as a postdoc to an extent that other fellows couldn't, because I had the funds I needed to buy equipment and get things going," she says. "So I have had a head start in launching my new laboratory. I still sometimes feel like a fish out of water, but fortunately my research is going well, and that makes it seem like there actually might be hope!"

When the lab walls seem to be closing in a bit too much, Dr. Schumacher takes off running. "I've been running for roughly 20 years now, without missing more than a day or two in row," she says. "I started for health reasons—running made me feel better." She has since been diagnosed as having type 1 diabetes, and she keeps running as a way to help control the disease.

"Running has another advantage, too," she says. "I get some of my best scientific ideas when I'm out there pounding away. If I'm bogged down in front of a computer, I go for a run and often come back with solutions I didn't think I would have come up with otherwise."

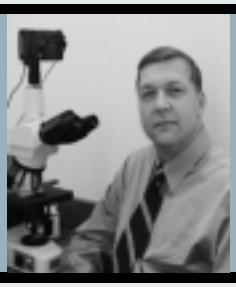
Defining, understanding, detecting, diagnosing, and treating communicable diseases have driven research since medical science began replacing medical art.

But now our microbes are becoming more and more resistant to antibiotics; new or unfamiliar diseases like Severe Acute Respiratory Syndrome (SARS) and West Nile Virus are appearing and expanding their range; and the threats of biological terrorism and biological warfare loom. BWF's support of work in the area of infectious diseases has always targeted understudied and undervalued problems. With more and more national resources earmarked specifically for work on the diseases that pose the clearest threat to public safety, the Fund's support of research that bridges gaps in understanding the central issue of infection —what happens at the interface between the human body and the microbes—becomes more critical than ever. BWF's dollars are helping to support a broader understanding of infection, an approach that both complements and stands apart from the current press toward practical engagement against a list of specific infectious agents.

In its 2000 strategic planning process, the BWF board made the decision to fold the Fund's five historical infectious diseases programs—the New Investigator Awards in Molecular Parasitology and Molecular Pathogenic Mycology, the New Initiatives in Malaria, and the Scholar Awards in Molecular Parasitology and Molecular Pathogenic Mycology—into a single new program focused entirely on understanding pathogenesis by supporting work at the many boundaries between pathogens and their hosts.

This year, we extended our support for work in infectious diseases to eight accomplished researchers, all of them assistant professors, through the Investigators in Pathogenesis of Infectious Disease program. Launched in the 2001/2002 grant cycle, the program has funded 8.3 percent of 205 applicants in its two years. The 17 Investigators in Pathogenesis join 55 awardees in parasitology and mycology supported through the Fund's New Investigators programs (which closed in 2001) as a strong and well-prepared generational cohort. We expect to see leading infectious disease research in the years to come.

In the hope of better understanding how the future will shape the field's needs, the Fund organized and supported a Banbury conference in Spring 2003, asking an eclectic group of researchers from within and outside traditional infectious disease fields to consider what is needed to form a more integrated understanding of pathogenesis. Those discussions, and ones that will follow in the upcoming year, will help shape the Fund's directions as the impacts of new diseases and new technologies continue to unfold.



Dr. Samuel Stanley, whose research has focused on the developing world scourge amebiasis, recently assumed the directorship of the Midwest Regional Center of Excellence for Biodefense and Emerging Infectious Diseases Research, one of eight NIH-funded centers across the country.

In Research on Amebiasis, Dr. Samuel L. Stanley Jr. Has Developed a Combination Vaccine Ready for Testing in Humans

Samuel L. Stanley Jr., first heard the word "epidemic" when he was six years old. His father, an anthropologist, was doing fieldwork in Indonesia when he decided to move the whole family from Urbana, Illinois, to Jakarta. "I remember hearing about the World Health Organization's efforts to eradicate malaria," says Dr. Stanley Jr., whose young mind somehow grasped the seriousness of the epidemic in his host country. Dr. Stanley, a 1999 Scholar in Molecular Parasitology, has been interested in the health problems of developing countries ever since, but it took a while for him to find his vocation as a physician-researcher in infectious diseases. He is a parasitologist and professor in the Department of Medicine at Washington University.

During the late 1970s, at Harvard Medical School, he intended to specialize in neurology and neurosurgery. But fate had something else in store; in his third year, he was one of four fellows chosen to participate in Harvard's collaborative program with the Albert Schweitzer Hospital in Gabon (formerly part of French Equatorial Africa).

As team leader and interim medical director of the hospital, the young physician saw hundreds of patients with malaria and tuberculosis, two of the world's deadliest infectious diseases. He and his colleagues also witnessed early evidence of a mysterious condition known locally as "wasting disease." It was 1978, and the human immunodeficiency virus (HIV) had yet to be identified.

It was clear to Dr. Stanley that he and his colleagues at Schweitzer Hospital were doing good by helping the sick, but equally clear that the region was hobbled by severe underlying problems. He saw infectious diseases running rampant amid conditions of poor sanitation and scarce health resources. Among the most devastating was amebiasis. An infection driven by the protozoan parasite *Entamoeba histolytica,* amebiasis, in the form of amebic colitis (inflammation of the colon) or amebic liver abscess, remains the second leading cause of death from parasitic disease worldwide. An invasive diarrheal disease, amebiasis thrives in countries where food and water are easily contaminated by human feces. But amebic infections aren't confined to the developing world; they are prevalent worldwide, though the mortality rate is much higher in the tropics.

Dr. Stanley's career-long research interest was shaped by his experiences in Gabon. For more than 20 years, he has investigated the nature of *E. histolytica,* the disease it causes, and the interactions between the potent pathogen and its human host.

During his residency at Massachusetts General Hospital, he met his future wife, fellow resident Ellen Li. The couple soon married and took fellowships at Washington University in St. Louis; he in immunology, she in gastroenterology. More than ever, Dr. Stanley wanted to pursue bench research on parasites and their hosts, and at Washington University, he found the ideal mentor in Joseph Davie, M.D., Ph.D., then chair of the Department of Microbiology and Immunology. Under Dr. Davie's guidance, he studied immunoglobulin genes and correlated their structure with their function.

After his postdoctoral work, Dr. Stanley was ready to strike out on his own, and amebiasis would be his prime target. He built on earlier studies suggesting that amebic proteins called lectins bind to carbohydrate-containing receptors on cell surfaces. The issue before him now was carbohydrate specificity—i.e., which sugars help the binding process along and which inhibit it. Using mutant Chinese hamster ovary cells, Dr. Stanley and his wife, coinvestigator Ellen Li, M.D., Ph.D., and a 1995 BWF Scholar in Toxicology, found that when galactose was exposed on the cells, they became more susceptible to amebic infection than when galactose was absent or masked by other sugar residues. The study, published in 1988 in the *Journal of Experimental Medicine*, demystified an important aspect of

host behavior in the presence of *E. histolytica* and explained why some people may develop symptomatic amebiasis while others don't—that it depends upon whether galactose is present or absent/masked in the human host's cells.

Soon, the Stanley lab was prepared to study host and parasite in tandem. How does the parasite fight for its turf? What factors allow it to cause disease? How do parasite and host exchange feedback along the way? These questions inevitably led Dr. Stanley and his team into vaccine research.

Because amebiasis is a disease of developing countries, there's no immediate incentive for the pharmaceutical industry to conduct clinical trials of a candidate amebiasis vaccine, Dr. Stanley says. Given financial constraints, he argues that an *E. histolytica* vaccine should be bundled into a combination vaccine that would target several intestinal diseases, protecting people from the diarrheal diseases that cause illness and death around the world and an especially high mortality rate among children.

The first steps toward developing such a combination vaccine have already been taken. "We were the first to have success with a recombinant amebic antigen," Dr. Stanley says. "Our challenge now is to take our vaccine candidate to the next stage, and that means testing it in humans."

Dr. Stanley is especially grateful for the unrestricted support he received from the Burroughs Wellcome Fund to carry out innovative research in an atmosphere of open-ended inquiry. "The Burroughs Wellcome grant encourages scientists to take risks," he says, "and the Fund's focus on tropical medicine has made an enormous difference in the quality and pace of research."

With the sequencing of the ameba's genome recently completed, the Stanley lab has been designing a microarray for studying what happens to the parasite at the molecular level when it attacks host cells. His research probes the relationship between structure and function, and he continues to clarify how the ameba's genes correlate with its virulent behavior.

Working at the interface of immunology, cell microbiology, molecular biology, and public health, Dr. Stanley was a good choice to direct the Midwest Regional Center of Excellence for Biodefense and Emerging Infectious Diseases Research (MRCE) based at Washington University in 2003. One of eight such NIH-funded centers across the country, the MRCE focuses on the poxviruses, a major potential threat to public health in the event of a bioterrorist attack. The goal is to develop the next generation of vaccines, therapeutics, and diagnostics that will protect the population from possible outbreaks of smallpox and other emerging infectious diseases.

Dr. Stanley welcomes the opportunity to carry out research that is directly linked to national security aims. But even if there's never another attack using a biologic agent, he says, the Midwest Center's research could lead to new findings that make a positive impact on health—and on science itself.

In the midst of his formidable responsibilities as an award-winning scientist, professor, and leader across several fields of research, Dr. Stanley still enjoys treating patients, and spends two months a year at Barnes-Jewish Hospital in St. Louis doing just that.

A purposeful life informed and defined by science. A coherent, important body of research. Multiple positions of professional leadership. A spouse who is a distinguished researcher. But among all these achievements, Dr. Stanley remains proudest of his four children. Ranging in age from eight to 18 years, they are a constant source of joy for their scientist-parents, who humorously describe their offspring as "our most successful recombinant DNA project."

If BWF's applicant pool is any indication, then there is clearly no lack of scientific talent attracted to the interface between biology and the theoretical and computational sciences.

In the second iteration of Career Awards at the Scientific Interface (CASI), the award rate was less than 10 percent. Seven new awards totaling $3.5 million were made this year to postdoctoral fellows—with Ph.D.s in physics, applied mathematics, chemistry, or biophysics—whose work addresses biological questions. Their predecessors, who received awards in 2001, are already transitioning to faculty positions at top-ranked research universities. Some of them are ending up in biology-oriented departments, while others are in mathematics or physics departments.

Before launching the CASI program, BWF funded three rounds of awards for institutional training programs, in 1996, 1998, and 2000. These programs now serve more than 150 graduate students and postdoctoral fellows. While career outcomes for these trainees will take years to emerge, early outcomes from two of BWF's longest-running programs predict a bright future for their participants. Sixty-one percent of the BWF Program in Mathematics and Molecular Biology alumni have gone directly to tenure-track faculty positions. Likewise, nearly 60 percent of the postdoctoral fellows from the La Jolla Interfaces in Science program are in tenure-track positions at research universities. Current comparative data on the rates at which physical science postdoctoral fellows enter academic careers is unavailable; however, fewer than 17 percent of 1995 chemistry and physics postdoctoral fellows were in tenure-track positions by 1997 (reference COSEPUP report on "Enhancing the Postdoctoral Experience for Scientists and Engineers").

Site visits to two of the programs, based at the University of Chicago and Johns Hopkins University, have confirmed the importance of independent funding for trainees in cementing new collaborations among investigators from different disciplines. While both programs are structured in ways that reflect their unique institutional milieu, the presence of these joint trainees is slowly changing the research culture. BWF has learned that cultural change, and not merely new institutional structure, is needed in order to sustain interdisciplinary careers in science.

In additon to the institutional training grants and career awards, BWF's Interfaces in Science program in 2000 made one round of Innovation Awards in Functional Genomics. These awards were made to accelerate the integration of the vast amount of genetic sequence and expression data into functional and clinically relevant insights into the physiology and mechanisms of human disease. Later, you will read more about one of the bright scientists BWF funded—Dr. Christopher Burge—now three years into his award.

Dr. Ryohei Yasuda: A Run of "Fortunate Bad Luck" Led Him from Physics to Biophysics and Imaging Single Protein Molecules

A glowing dot spinning like a dervish features in the movie Ryohei Yasuda made as a graduate student. Though by no means a Hollywood production, Dr. Yasuda's film is an elegant sight to biologists.

The reason for the movie's allure is that it vividly portrays the rotation of a single protein enzyme, which Dr. Yasuda cleverly tagged with a much larger protein complex and imaged the resulting motion through a microscope. In so doing, he revealed the detailed spinning mechanism of one of only two rotary engines known in nature—the other being the molecular motor that powers the spinning, whiplike flagella of bacteria.

Dr. Yasuda's achievement in imaging the enzyme, called F1-ATPase, while he was still working on his Ph.D. at Keio University in Japan, illustrates the creativity that the young biophysicist has brought to his research. Now a postdoctoral researcher at Cold Spring Harbor Laboratory, he is a 2003 recipient of a Burroughs Wellcome Fund Career Award at the Scientific Interface.

Working in the laboratory of Dr. Karel Svoboda, Dr. Yasuda uses sophisticated imaging techniques to actually see the interactions of single protein molecules. His quarry are the proteins that form the machinery in "dendritic spines," the infinitesimal bristles that stud the surface of nerve cell structures called dendrites.

These spines are the critical receiving and amplifying stations for chemical signals from neighboring neurons and are responsible for triggering the impulses that drive all nervous

system function. Once triggered, the protein machinery in these spines opens porelike channels in the neuron's surface membrane that enable cations (mainly sodium) to flow into the cell to generate the electrical signal. Calcium influx into the spines triggers a number of cascades of biochemical reactions between proteins, leading the reorganized protein machinery to regulate the efficiency and strength of the electrical signal transmissions. These signalings underlie network plasticity—and ultimately, learning and memory.

"These dendritic spines are really small, and they often contain only a few copies of a given protein," Dr. Yasuda says. "So, it requires a single-molecule-level imaging technique to really figure out what these molecules are doing."

Dr. Yasuda has his work cut out for him, because these tiny compartments, called the "postsynaptic density," consist of hundreds of proteins. It is the chemical reactions that occur when these proteins grab and release one another that constitute the biochemical signaling pathways in the dendritic spine. And it is these pathways that underlie learning, memory, and perhaps other brain functions in animals, including humans.

The problem with understanding these pathways, says Dr. Yasuda, is that no other analytical technique can reveal interactions between proteins. "Many molecular biologists are trying to understand signaling in the postsynaptic density by knocking out a particular protein or activating a particular protein," he says. "While this helps understand which proteins are involved in a pathway, it can't tell you about how the protein works and how the protein interacts with other proteins. Also, the commonly used biochemical techniques of measuring the reactions between these proteins won't work, because these compartments are so small. So, I think imaging is really the optimal way to study the postsynaptic density. We really need to see the interactions between each molecule in response to calcium influx."

Dr. Yasuda uses a physical phenomenon that occurs between two fluorophores, called "fluorescence resonance energy transfer," or FRET, to see such molecule-level interactions. By attaching different fluorophores to each of two proteins and measuring FRET between the fluorophores, he can study interactions of these proteins. To make sure the proteins are behaving as they naturally would in real tissue, Dr. Yasuda performs his experiments on slices of rat brain. Using a microscope that shoots a laser beam of a specific wavelength into the brain slice, he can excite just one of the two fluorophores to produce light and then measure precisely how that "donor" fluorophore transfers its energy to the "acceptor" fluorophore on the other protein.

The efficiency of FRET depends on the distance between the two fluorophores, Dr. Yasuda says. FRET is efficient only when two fluorophores are within nanometers—about the size of proteins. Therefore, by monitoring FRET efficiency, he can study whether two labeled proteins bind to each other. Also, it is possible to calibrate distance between two fluorophores to determine how they interact.

The process is like studying how one runner in a relay race hands off the baton to another: the hand-off process can reveal important information about how the two runners are performing. Similarly, by studying the efficiency of the hand-off process between the paired proteins, Dr. Yasuda can glean critical information about how the two proteins are interacting. So exacting are Dr. Yasuda's techniques that he can now measure quantitatively FRET in the two proteins—a technique he calls "two-photon fluorescence lifetime imaging microscopy."

Dr. Ryohei Yasuda's basic research on the protein machinery within the dendritic spine could lead to the development of drugs for mental disorders or drugs that could enhance memory or other neurological functions.

These techniques promise to yield a far more detailed understanding of the protein machinery within the dendritic spine. And although his work is basic, Dr. Yasuda says such improved understanding could lead to development of drugs for mental disorders or drugs that could enhance memory or other neurological functions.

Dr. Yasuda emphasizes that BWF's award has proven crucial in helping him launch his career. "First of all, it has given me confidence that I am able to do work in the United States," he says. "I'm now seeking a faculty position, and this also gives me

a credential that will help me in that search, as well as initial funding to set up my own laboratory."

Dr. Yasuda was not always interested in biophysics, but it was a remarkable run of what he calls "fortunate bad luck" that led him into the field. "I was a physics student as an undergraduate and didn't even think about biophysics," he recalls. "Then, in my fourth year, we had to get into a lab to do our thesis. I had chosen particle theory, but there were too many applicants for that lab, so they held a lottery, as was the tradition. I lost. My second choice was a semiconductor lab, but I also lost that lottery. The biophysics lab was my tenth choice, and since there were only ten labs, I did get that one."

However, in that laboratory he saw a sight that fascinated him—a movie of the action of a tiny molecular "superhighway" in the cell called an actin filament. Such actin filaments are not only the molecular paths along which cargoes of molecules are transported within the cell. They also are one of the basic structures of the muscles that power movement.

"In the biophysics lab, the professor showed a beautiful movement of actin filaments across a surface, like a worm crawling on a plate," recalls Dr. Yasuda. "I became fascinated by this movement, because even though you couldn't say these proteins were really 'living,' they were intermediate between living and nonliving stuff. So, I became a biophysicist because I wanted to know how these proteins work, in contrast to a biologist, who wants to know what proteins do."

When he is not pondering the elegance of protein interactions, Dr. Yasuda is making elegant music. An accomplished harpsichordist and pianist who began his training at age five, he prefers to play the early Baroque music of Bach, Mozart, and Beethoven. He met his wife, a classical violinist, in an ensemble class and they play duets regularly. They have three children, ranging from five months to six years old, and Dr. Yasuda reports that they have thoroughly adapted to American schools and culture.

He has recently had to restrict his playing to the piano, because "when I came to the United States three years ago, I had to sell my harpsichord," he says. "But if I get a faculty position, one of the first things I want to do is buy a good harpsichord."

Dr. Christopher Burge: Deciphering How Genes Are Stitched Together

Nature can be very, very messy. The living cell, for example, was historically viewed as a smooth-running biological clockwork, efficiently transcribing its genetic information from DNA to messenger RNA (mRNA), which provides the template for making proteins. Biologists once believed that the path from DNA to mRNA to protein was a straightforward one. No such luck.

> Instead, scientists have realized, to their utter surprise, that the cells of higher organisms work like manic film editors—a sort of genetic Edward Scissorhands.

The cell's RNA splicing machinery relentlessly snips apart and sticks together bits and pieces of the initially transcribed "pre-mRNAs," to arrive at the final cut of the mRNAs that code for the molecular masterpieces that are working proteins.

An important challenge for biology, believes Dr. Christopher Burge, recipient of a 2000 Burroughs Wellcome Fund Innovation Award in Functional Genomics, is to understand the intricate machinery of the cell's mRNA "film editor." "The vast majority of genes in the human genome have to be spliced in order to be expressed," says Dr. Burge, an assistant professor of biology at the Massachusetts Institute of Technology. "So, it's a basic process, in the same way that translation of mRNA into proteins is a basic process. The difference is that the rules for translation were worked out 40 years ago, but the rules for splicing are still not well understood."

Understanding these rules will have a profound impact on our understanding of how the genome shapes the set of proteins expressed in each human cell. "For example, a major paradox arising from the Human Genome Project was that there appeared to be only about 30,000 genes in the human genome—about 50 percent more than in the simple round-

worm *Caenorhabditis elegans*," Dr. Burge says. "This worm has only around a thousand cells and a very primitive nervous system. So, somehow humans achieve far more complexity with only about 50 percent more genes."

The secret may lie in a version of the mRNA processing pathway known as "alternative splicing," in which the cells use their splicing machinery to create multiple distinct proteins from the same gene. "One fairly straightforward result arising from analysis of the human genome sequence was that at least half of all human genes appear to be alternatively spliced," Dr. Burge says, "and such splicing isn't limited to producing two different variations. For some genes, there are hundreds or even thousands of different combinations of segments that can be spliced together, potentially making thousands of different mRNAs—and therefore thousands of different proteins from a single gene. So, alternative splicing is an important mechanism that allows the human genome to express huge numbers of different proteins, which contributes to the complexity of humans."

Dr. Christopher Burge, center, says an estimated 15 percent of all mutations that cause human diseases do so by disrupting the splicing of messenger RNA (mRNA) from affected genes. On his left is Dr. Phillip Sharp, Nobel Prize winner and BWF awardee.

Understanding the rules of splicing could also have profound impact on treatment of disease. "It is estimated that about 15 percent of all mutations that cause human diseases exert their effect by disrupting the splicing of mRNA from affected genes," Dr. Burge says. Such genetic disorders include blood, metabolic, and neurological diseases. "So, if we could understand the rules involved in splicing, then perhaps we could manipulate the process with drugs or other treatments to cause the cell's machinery to recognize the mutated gene segments and restore normal splicing."

The splicing machinery of higher organisms recognizes two kinds of gene segments: exons and introns. "If you think of the process as analogous to film editing, the exons are the good takes that you keep and put together to make the final cut, and the introns are the scraps left on the cutting room floor," Dr. Burge says.

And like any good editor, the splicing machinery recognizes where cuts need to be made, in part by using as guides specific sequences of RNA units, called ribonucleotides, that mark the boundaries of exons and introns. The machinery is stunningly accurate. "This machine has to cut and paste exons at exactly the right nucleotide," Dr. Burge notes. "If it is off by just one nucleotide, it shifts the reading of the mRNA and makes completely the wrong protein. And we believe the cellular splicing machinery probably gets it right about 99 percent of the time, despite the fact that the guide sequences are highly degenerate and so there are far more potential splicing sites than are actually used."

Initially, in his graduate work in the mathematics department at Stanford University, working with Dr. Samuel Karlin, Dr. Burge developed a widely used computer program called GENSCAN that predicts the locations and exon-intron structures of genes in the human genome, in part by modeling the guide sequences used by the splicing machinery. During his postdoctoral work at MIT, in the laboratory of Nobelist Dr. Phillip Sharp—who shares the BWF innovation award—Dr. Burge worked to figure out how the splicing machinery recognizes and uses those sequences with such uncanny precision.

Recently, Dr. Burge and his colleagues developed a statistical approach to recognize sequences called "exonic splicing enhancers" (ESEs) that are embedded in exons and that both code for proteins and enhance the splicing machinery's ability to recognize that exon. "Mutations in these exon splice enhancers are common in genetic disease," he explains. "When they're mutated, the splicing machinery often skips over that exon,

leaving it out of the final mRNA, and making a defective protein. "Based on that work, we predicted a set of exonic splicing enhancer motifs. And when we tested these sequences, in collaboration with Dr. Sharp's lab, we found that all of them did, indeed, function as splicing enhancers in cultured human cells.

Dr. Burge and his colleagues applied their knowledge of ESEs to understanding mutations in the gene associated with Lesch-Nyhan syndrome, a genetic disease characterized by bizarre movements, joint swelling, and such abnormal behaviors as chewing off fingertips and lips. "The mutations were known to cause skipping of particular exons in the affected gene, and we showed that about half of the mutations that caused such skipping disrupted our predicted ESE sequences," he says.

In addition to searching for more ESEs, Dr. Burge is now looking for "protein splicing factors" that link the splicing machinery with particular ESEs. In addition, he is searching for the opposite of ESEs, called "exonic splicing silencers" (ESSs), which block exons from being included in proteins. ESSs may well be a key to alternative splicing, enabling the splicing machinery to swap out particular exons and create different proteins from the same gene.

In another major effort, Dr. Burge and his colleagues are exploring the mysterious functions of so-called "microRNAs," tiny RNA molecules that regulate the function of other genes. In collaboration with the laboratory of Dr. David Bartel, they have developed algorithms to identify microRNA genes in genome sequences and, recently, developed a method to predict which genes are regulated by any given mammalian microRNA. These studies have led to the conclusion that microRNAs in mammals are controlling a much wider range of biological processes than was previously suspected.

It's not surprising that Dr. Burge has immersed himself in the stunningly complex task of decoding the cell's genetic control machinery. He recalls bring fascinated with codes since he was a boy. "I remember reading a science fiction novel describing how a message from extraterrestrials had been received, and how scientists worked on figuring out what it meant," he says. "I remember thinking that if such a message was ever received, I wanted to be the guy they called to figure it out.

"Since there haven't been any such messages, it wasn't a very practical career path," he adds. "But when I realized that there would be all these genome sequences coming out that were like messages that needed to be decoded, it had the same kind of appeal. It's a kind of language to figure out, but one that is unlike any human language, and that challenge motivated me to use computational methods to tackle the DNA code and figure out what the DNA was trying to tell us."

This fascination with both mathematics and biology led him to a B.S. degree in biology and a Ph.D. in computational biology at Stanford, and ultimately to his career at MIT. Outside the laboratory, he also has been an explorer of strange terrain. After his undergraduate education, he worked with the World Health Organization in Nicaragua to improve medical care there. And, his travels have taken him in search of exotic wildlife in the Galapagos, Costa Rica, and Glacier National Park.

These days, he embarks on adventures of another kind, as he and his wife enjoy taking their one-year-old daughter for treks in the Massachusetts woods. "She was born in mid-November, when it's cold, and she is totally comfortable being outside in any weather," Dr. Burge says. "So, we bundle her up, put her in the backpack carrier, and take her to woods and farms, where she can see all the animals."

In its 2000 strategic planning process, the Fund's board decided to close its remaining programs in the pharmacological and toxicological sciences, all of them New Investigator Awards aimed at assistant professors. Earlier Scholar Awards in the pharmacological and toxicological sciences were retired in the late 1990s. A number of excellent young investigators, granted awards before the programs closed, will be supported by BWF for several more years.

Dr. Carla Koehler: Studying Yeast Yields Important Data on How Human Cells Generate Energy

Dr. Carla Koehler wants to know how the energy factory in every human cell assembles itself, and how that construction sometimes goes awry. Armed with this knowledge, it may be possible to design new drugs to correct the operational defects and, in the process, treat or prevent a host of diseases.

"All cells contain several hundred mitochondria—complex protein structures that produce most of a cell's energy and perform various other vital functions," says Dr. Koehler, a 2000 recipient of a Burroughs Wellcome Fund New Investigator Award in the Toxicological Sciences and an assistant professor of chemistry and biochemistry at the University of California-Los Angeles. "We are trying to understand the basic mechanisms of mitochondrial biogenesis, the process by which these powerhouses are constructed within cells, and also how one particular aspect of this process sometimes malfunctions to cause disease."

Dr. Koehler focuses on how the inner of two membranes within mitochondria are constructed from proteins imported from the surrounding cytoplasm. "Very little is now known about the assembly and function of this inner membrane," she says. "This is still an area ripe for experiment and discovery."

Building on work she began as a postdoctoral fellow, she uses biochemical and genetic techniques to probe the details of mitochondrial biogenesis in *Saccharomyces cerevisiae*—baker's yeast. "The process in yeast is very similar to that in humans, so this provides a useful model system," she says. "Plus, it's easy to grow lots of yeast, manipulate the cells genetically, purify lots of their mitochondria, and then apply a variety of biochemical tests to tease out the information we want."

Of key importance, Dr. Koehler has identified a novel process that yeast mitochondria use in importing proteins and assembling their inner membranes. She also has shown that a specific genetic mutation in one of the components of this process causes a disease in humans—Mohr-Tranebjaerg syndrome—that leads to blindness, deafness, and an inability to move properly. "The cause of this disease had previously been unknown," she says. "This is the first disease that has been directly attributable to a defect in the protein transport process that occurs in the inner membranes of mitochondria. So this really is opening a new field."

Dr. Koehler also studies cells taken from patients with the disease, working jointly with one of the disease's experts, Dr. Lisbeth Tranebjaerg of the University of Tromso, in Norway. "What's particularly interesting is that we have identified additional patients with two other diseases that we suspect are caused by defects in mitochondrial protein transport," Dr. Koehler says. "One is a type of cancer and the other is a type of Tourette's syndrome, and we will be expanding our studies to include cultured cells from these patients as well."

To build on these efforts, Dr. Koehler has been working to develop a mammalian model, using genetically engineered mice, for probing this novel protein transport process. "We can knock out a gene in mice in order to make them develop the disease," she says. "Then we can study the mitochondria of the mice to better understand the fundamental molecular defects that give rise to the disease. Working in mice is slower and more difficult, but this will give us the opportunity to test the ideas that we gain from our work with yeast and cell cultures."

The long-term goal of Dr. Carla Koehler's research is to learn enough about mitochondrial biogenesis to be able to develop new drugs or other therapies to fight diseases such as cancer, Parkinson's, and Alzheimer's—all caused in part by mitochondrial malfunctions.

Her group engineered a strain of mice that showed early promise but ultimately were unsuitable. "So we're back to square one, in a sense," she says. "But we learned a lot with our initial mouse model, and we hope to be able to apply this information in developing a new strain that has all the characteristics we need."

The long-term goal is to learn enough about mitochondrial biogenesis to be able to develop new drugs or other therapeutic methods to fight disease. "We've only scratched the surface here," Dr. Koehler says. "We already know of many diseases, including cancer, Parkinson's disease, and Alzheimer's disease, that are caused at least in part by mitochondrial malfunctions, and I believe that many other diseases—some common, some less so—will ultimately be linked to such problems. Finding drugs to treat these diseases will take a long time, but we won't be able to really begin searching seriously until we've gained a better understanding of how mitochondria work."

Growing up on a dairy farm in Wisconsin piqued Dr. Koehler's interest in science. "I always seemed to be interested in how you might use genetics to breed cows that give more milk or have other desirable traits," she says. Her farm-nurtured interests prompted her to major in biochemistry in college. She earned a B.S. from Iowa State University and then spent a year studying to become a veterinarian. "But I quickly found that I was more interested in basic research, so I switched back into biochemistry. I studied mitochondria in dairy cattle as part of my work for my master's degree, and then for my doctorate I worked on developing more general models of how mitochondria function." Along the way, she also received several Iowa State University Teaching Excellence awards.

Following her graduation in 1995, Dr. Koehler headed abroad for postgraduate work. "I studied with Dr. Gottfried Schatz at the University of Basel, in Switzerland—maybe not so far afield from Wisconsin's dairy farms after all," she says. "That's where I first identified the protein import pathway in yeast that we are continuing to study in order to better understand mitochondrial biogenesis."

Dr. Koehler moved to UCLA in 1999 and says her BWF award was instrumental in advancing her research. "The award was especially important in enabling me to extend my research into mammalian systems," she says. "I didn't have a long track record of working with mice, and so I lacked the preliminary data that the National Institutes of Health and most other granting agencies want to see. The award let me get my feet wet, based on the promise of my earlier work with yeast. As we've steadily gained experimental data, we have been able to win additional funding that will help us to continue these studies." She now receives support from the National Institutes of Health, the Muscular Dystrophy Association, and the Beckman Foundation, among others.

"BWF's award has helped me make the critical transition from starting up my own laboratory to becoming an 'established investigator' among my peers," she says. "Based in large part on the research supported by the award, my department has recently nominated me for early tenure."

She has reached another milestone as well: "My first four Ph.D. students are now going on to accept postdoctoral positions in other labs," she says. "I'll be very interested to watch their continued progress."

Dr. Koehler stays in high gear both inside and outside the lab. "When I'm not in the lab, I'm usually on my bike," she says.

Her bicycle has taken her into the world of elite racing: she's the current national champion in the U.S. Cycling Federation's Masters Team Pursuit event, which pits four-person teams of riders over age 30 against each other for a two-kilometer race on a cycling track. Not only did her team win, but Dr. Koehler also won the individual championship. In addition, she pedals in national competitions for a team sponsored by Minute Maid and Dasani. "We race to win, of course," she says. "But we're also trying to develop some younger women who will go on to ride for the U.S. national team or the Olympic team."

In the community, Dr. Koehler periodically teaches science to third-graders in an inner-city school. "One of the members of my bike team teaches there, and she told me about the almost total lack of science education offered in her school," she says. "So I've been going into her class and giving the kids presentations on microbiology. They seem to like it—and I know I do."

The long-term goal is to learn enough about mitochondrial biogenesis to be able to develop new drugs or other therapeutic methods to fight disease.

Discoveries in Dr. Rama Ranganathan's lab may have important clinical implications, such as the ability to design targeted inhibitors and activators of protein drug targets that can affect one biological process and not others.

Dr. Rama Ranganathan Combines Expertise in Engineering and Biology to Probe the Complex Machinery of the Cell

"Let's say you were an alien from outer space, and you had nothing but pictures of an automobile," declares Dr. Rama Ranganathan. "Would you know what it did? How the motor, the drive train, and the wheels worked? Even though the pictures help you a lot, without watching it function, you couldn't understand how it works."

By the same token, he adds, to really understand how the intricate protein networks that constitute the machinery of life function, science must advance beyond the current static three-dimensional structures of proteins.

Recipient of a 1998 Burroughs Wellcome Fund New Investigator Award in the Pharmacological Sciences, Dr. Ranganathan has joined in the effort to develop the basic principles that will explain the dynamics of the cell's protein machinery. Combining his knowledge of engineering and biology, he wants to find quantitative theories to explain how proteins "communicate" with one another as they function in the signaling pathways that make up the cell. For example, protein enzymes catalyze the biochemical reactions of life's machinery; and protein hormones, receptors, and pore-like ion channels work at cell surfaces to transmit signals from cell to cell.

"When I started my laboratory, I identified two basic problems I wanted to work on," explains Dr. Ranganathan. "One problem was understanding how the networks of atoms that make up proteins have the properties that make signals go through proteins and from protein to protein. And the second problem was roughly one resolution level up: how does the network of proteins that we call the signaling system in cells make it possible for information to flow from the cell membrane to gene expression in the nucleus, for example?"

To solve these two problems, Dr. Ranganathan has divided his laboratory at the University of Texas Southwestern Medical Center—where he is an associate professor of pharmacology and a Howard Hughes Medical Institute associate investigator—into two complementary groups. One group uses statistical methods together with experiments to explore how the structure of proteins determines their dynamic properties—like exploring how the structures of a car engine's valves, pistons, and ignition determine their function. The other group uses genetic and biochemical techniques to study how networks of proteins communicate with one another in functioning pathways—like exploring how an engine's components interact to make an engine run.

In the latter effort, Dr. Ranganathan uses photoreceptor neuronal cells in the fruit fly as his model system—his test vehicle, so to speak. "The fly photoreceptor cell is a beautifully suited system for working out the quantitative picture of signaling," he says. In those photoreceptor cells, light activates photoreceptor proteins on the cell surface, triggering the cell to generate an electrical signal that travels to the brain. Importantly, "we can use the powerful techniques of genetics to alter these proteins at will," he says, "and this enables us to tease apart the mechanisms of the photoreceptor cell."

In this way, the researchers selectively alter proteins in the photoreceptor cell by mutation to understand how the proteins work together—like altering the shape of a piston to explore the effect on a car engine's function. To understand the function of individual proteins, they also use x-ray crystallography to obtain detailed three-dimensional images of their structure. (In this technique, researchers direct x-ray beams through crystals of a target protein and analyze the resulting intricate pattern—as the protein's atoms diffract the beam—to arrive at a structure.) Finally, the scientists perform detailed measurements of the electrical properties of the photoreceptor cell to understand how the cell's internal machinery affects its electrical signaling.

The scientific strategy that defines Dr. Ranganathan's laboratory involves using the vast number of "experiments" that evolution has performed on cellular machinery to understand basic principles underlying that machinery.

"If we tried to make all the mutations needed to totally understand the problem of information flow in proteins, we'd be long dead and gone before we even got to a tiny fraction of the number of mutants we'd have to study," he says. "So, we realized that other scientists had determined the sequences and structures of proteins of like function found in a range of species. It seemed to us that by studying the evolution itself of the diversity of proteins, we ought to be able to extract statistical measures that tell us about how the amino acids that make up protein molecules interact with each other."

For example, he says, by statistically comparing how a protein with a given function varies across species, he and his colleagues can develop theories about which features of that protein are critical for its function. Then, they can test these theories by precisely altering the same proteins and studying them in both test tubes and the fly photoreceptor cells. In this way, he says, "We can ask our beautiful model system, if I made mutations on these sites that we predict from this evolutionary analysis to be critical for information flow, do we, in fact, disrupt vision in flies?"

BWF's support has been key to this daring effort at "comparative proteomics," he says. "The Fund's grant has had an enormous impact, because it allowed us to do things that ordinarily would be considered highly risky and daring that we couldn't do with the usual grants. We could support some extremely talented graduate students and obtain critically needed computer equipment to enable us to do computational analyses critical to advancing our theories."

Also, he says, BWF's support enabled his team to test theories of how evolution influences protein structure by actually building artificial proteins to demonstrate that influence.

Besides advancing basic understanding of biology, discoveries in his laboratory may have important clinical implications. "First, it should aid in predicting the sites of mutations that make people vulnerable to disease," he says. "And secondly, it should help us in the process of achieving the Holy Grail of pharmacology—designing highly targeted inhibitors and activators of protein drug targets that can affect one biological process and not others. And, these drugs could work quickly and reversibly in a beautifully controlled way."

Dr. Ranganathan's background and training have prepared him well for applying the highly quantitative principles of engineering to biology. Beginning his undergraduate career at the University of California at San Diego, he transferred to the University of California at Berkeley to study bioengineering. There, he focused on control systems—the quantitative principles that explain the behavior of networks of components, ranging from automobile cruise control to train schedules. His fascination with biology also led to undergraduate research in biology at the University of California at San Francisco, where he studied a genetically engineered mouse strain that mimics the abnormalities of Down's syndrome. He applied his engineering background to quantitative analysis of the congenital heart defects in such mice, revealing that what seemed like complex abnormalities actually arose from a single physiological defect.

Such experience also put him in an ideal position to explore the still embryonic field of systems biology. "The concept of systems biology wasn't even close to being on the radar," he says. Determined to help pioneer the new approach to biology, he completed an M.D./Ph.D. program back at the UC San Diego that has since put him in the forefront of what he sees as an extraordinarily challenging field.

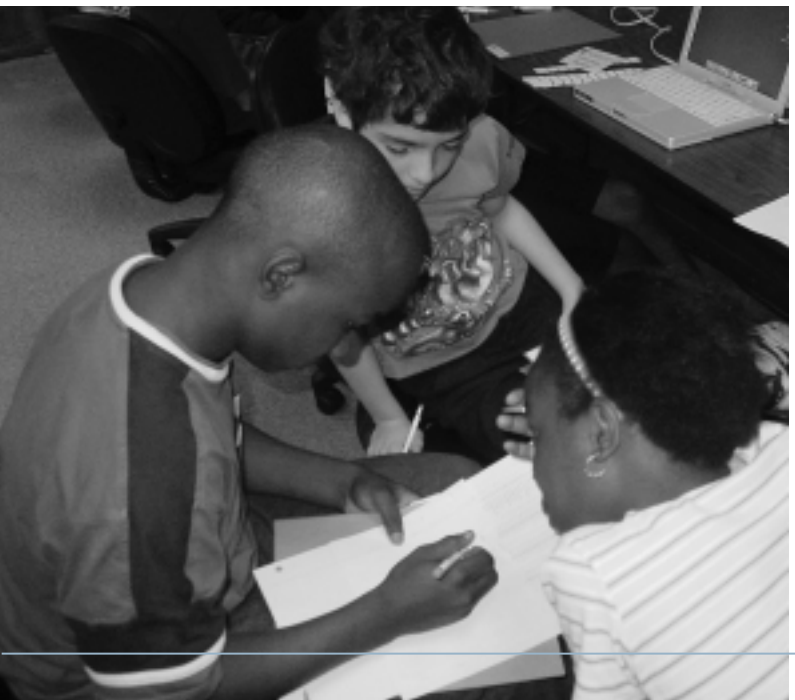
"In engineering, we have these established mathematical principles that let engineers make a cruise control or an artificial vision system, and that let you predict their behavior" he says. "But in biology, the systems are amazingly complicated and rich. The problem with applying engineering principles to biology is that we engineers have to impose constraints on the parts of systems, because we don't want to deal with the vast complexity that's possible. We generally try to limit ourselves in engineering to linear, time-invariant systems. But biological systems are exactly the opposite. They are nonlinear and definitely time-varying. I want to develop a new body of theory that will describe control behavior in nonlinear, time-variant biological systems."

Outside the laboratory, Dr. Ranganathan is known for his nonlinear, time-variant hobby of playing rock and jazz guitar. Although he has played since he was six, his music has recently taken a back seat to his wife and two children, a boy six and a girl nine, and his academic career. But he still plays as often as he can and enjoys camping out with his kids, teaching them sports and coaching their soccer team.

Through a pilot initiative called the Teacher Link Program, a group of retired and working scientists, mathematicians, engineers, and technologists have been trained in the latest inquiry-based science curriculum for pre K-12 students, informed about educational standards in science, and deployed to assist teachers who want help.

The Teacher Link Program (TLP) is the brainchild of the newly created North Carolina Science, Mathematics, and Technology Center (SMT Center), which recruited and matched TLP scientists with teachers who need expertise in SMT education. Teachers typically do not have time to reach out to the community for assistance, so the TLP reaches out to teachers, serving to invigorate teaching and enhance student learning. The TLP is a partnership between the SMT Center, North Carolina school systems, Duke University Center for Inquiry Based Learning, Sigma Xi, and the Burroughs Wellcome Fund.

BWF created the SMT Center to systematically improve performance in SMT pre K-12 education. Dr. Sam Houston, a longtime education and community leader, was selected to head the Center. The TLP is one of many initiatives the Center is pursuing to ensure that all children in North Carolina are equipped with knowledge and skills in the sciences.



Investing in developing the careers of young scientists is central to BWF's mission; however, the Fund recognizes that one of our major challenges is finding ways to encourage young people to pursue careers in science. The Student Science Enrichment Program was BWF's initial effort to engage and excite students, particularly underrepresented minorities and women, in science learning and to encourage them to pursue science careers. Our efforts are noteworthy: since the program was launched in 1996, we have reached more than 23,000 middle- and high school students in North Carolina. Despite the program's success, we soon realized that enrichment alone was not enough, so we began building a host of ancillary activities to improve learning, including supporting teacher training in advanced science and mathematics courses through cyber campuses across the state. This program is a good start, but we need to do more.

Our students must compete globally, so we must offer them a quality education second to none. Taking a hard look at our educational system always involves policy issues. In the United States, students have 180 days of classroom instruction. In other industrialized countries, students spend much more time in structured learning. South Korea, for example, has a school year of 220 days. Nearly 85 percent of Korean students are enrolled in night courses where they typically receive an additional two to three hours of instruction in advanced SMT and language courses and learn to take standardized tests. Since 1996, BWF has supported the North Carolina Institute for Education Policymakers to study education policy issues. We offer state legislators an opportunity to study educational systems in other states and abroad to learn firsthand what works best for students and teachers.

To get hands-on experience in how computers code and decode messages, students in the 2003 Internet Science Explorations workshop, given by the Shodor Education Foundation, created short messages in ASCII (American Standard Code for Information Interchange) using ASCII charts for coding.

In fiscal year 2003, BWF made six new Clinical Scientist Awards in Translational Research, bringing the total number of awardees in this program to 52 and the total investment to $39 million.

As mid-career mentors for the next generation of physician-scientists, this group represents an endangered species: investigators capable of translating basic science insights into clinical application, and translating clinical questions back into hypotheses that can be explored in the laboratory. In February, BWF convened the 10 awardees for 2000 for a mid-course progress report and to ask them about obstacles to sustaining translational research within their academic health centers. Their responses regarding what is needed were as follows:

- Research experience for medical students (As the number of graduating medical students interested in research careers has diminished, the number of Ph.D. graduates interested in research has risen).
- Greater integration of clinical concepts in Ph.D. training and better structures for professional development of Ph.D.s who are appointed in clinical departments. Clinical research training programs targeted for Ph.D.s would be an obvious solution, but only if there were clear career paths, including opportunities for leadership for graduates of such programs.
- Professional and specialty societies to develop resources that would nurture research careers. To this end, BWF has supported the Clinical Research 2001, 2002, and 2003 meetings. These meetings are jointly organized by the American Federation for Medical Research, the Association for Patient-Oriented Research and the directors of the NIH-funded General Clinical Research Centers and K-30 Clinical Research Training programs. This meeting aims to spotlight the best in patient-oriented research, provide trainees with an opportunity to present their work in an interdisciplinary (i.e., not disease-specific) forum, and provide career development resources for trainees and new investigators in clinical research.

In order for their efforts at translation to thrive, these talented investigators depend upon a complex ecosystem, which includes academic medical centers, basic scientists, allied health professionals, pharmaceutical and biotech companies, clinical trial participants, federal and private funders, regulatory agencies, and even health insurers. Recognizing this, BWF has remained involved in the Clinical Research Roundtable, based at the Institute of Medicine of the National Academy of Sciences. The Roundtable, chaired by BWF President Queta Bond, seeks to promote collaborative solutions to system-wide barriers that cannot be effectively addressed by any one stakeholder in the enterprise. In that spirit, BWF has also provided leadership during the past few years within the Clinical Research Alliance, a loose affiliation of private foundations and voluntary health agencies. Through shared intelligence and best practices, as well as coordinated communication with the National Institutes of Health, the group has a common goal of developing the clinical research workforce and removing any barriers that might impede the progress of their work.

Dr. Matthew Warman: Searching for Malfunctioning Genes That Cause Inherited Joint Disease

The young athletes whom Matthew Warman coaches on his son's baseball team probably don't realize their coach is acutely aware of potential damage to their growing joints as they run, jump, throw, and catch. In his day job, Dr. Warman—recipient of a 2000 Burroughs Wellcome Fund Clinical Scientist Award in Translational Research—works to understand how to keep ankles, knees, fingers, and elbows healthy. His studies of rare inherited joint diseases have given him unique insights into how joint function can go awry, as well as possible new pathways to treatment.

Because the disorders he studies affect children's joints after birth, insights from his research also could help the parents and grandparents cheering in the stands avoid common forms of arthritis.

Dr. Warman and his colleagues at Case Western Reserve University, where he is an associate professor and a Howard Hughes Medical Institute assistant investigator, focus on rare joint diseases with mouth-filling names—camptodactyly-arthropathy-coxa vara-pericarditis syndrome, and progressive pseudorheumatoid dysplasia—mercifully abbreviated CACP and PPD. Children born with CACP show minor deformities of their fingers but are otherwise healthy. However, their growing joints tend to swell, with overproliferation of the cells that surround the space between the joints—the synovium. The result of such overgrowth is that people with CACP suffer joint failure much earlier than others, requiring joint replacement surgery as early as their thirties.

Children born with PPD also appear normal at birth. "But between three and five years old, they seem to slow down in their activity levels, compared to their peers," Dr. Warman says. "They don't run as fast, they seem to tire out a little bit more, and they act a little achy." Although the symptoms are often misdiagnosed as juvenile rheumatoid arthritis, X-rays reveal "that there is something wrong with the structural components that make the joints, as opposed to an autoimmune process that damages the joints, as in rheumatoid arthritis," he says.

In searching for the malfunctioning genes underlying these and other such joint diseases, Dr. Warman perceived not only an opportunity to help affected children, but also a route to understanding how joints maintain and repair themselves. "My laboratory has focused on conditions in which children are born quite healthy, but as they get older they develop symptoms," he says. "And we focus on these diseases because we know the genes that are disrupted are those important for postnatal maintenance of bones and joints, as opposed to prenatal development. So, the biological pathways involved are those that are not just necessary for those affected children, but for the maintenance of bone and cartilage in all of us as we get older."

Thus, he says, "if the pathways are common between people with the rare inherited diseases and those with such common acquired disorders as osteoarthritis and rheumatoid arthritis, we can work toward treatments that will affect these pathways and help both kinds of people."

Dr. Warman and his colleagues have made advances toward understanding both CACP and PPD by pinpointing

Dr. Matthew Warman studies inherited disorders affecting children's joints after birth; insights from his work may also help adults suffering from arthritis.

Dr. Warman and his colleagues have made major strides in understanding yet another skeletal disease, acromesomelic dysplasia, Maroteaux type. In identifying the gene underlying this inherited failure of bone growth, the researchers believe they might have hit upon a pathway for treating growth disorders in children.

the malfunctioning genes that cause these conditions. The scientists also have developed genetically altered mouse strains lacking the genes, and having such models available will be critically important in understanding the disease mechanisms. For CACP, these "knockout mice," which lack the gene for the protein lubricin that seems to be a key for smooth joint function, have proven to be clear animal mimics of the disorder. "Mice lacking this protein seem to have extra sticky cartilage," says Dr. Warman. "So, that tells you that the cartilage isn't lubricated as well, and doesn't glide frictionlessly against itself in a joint." The altered mice also exhibit the telltale overgrowth of the synovial cells, as do human CACP patients.

Now, Dr. Warman and his colleagues are working to engineer an even more advanced "inducible promoter" mouse model of CACP, in which they can switch the gene for lubricin on and off at will during the mouse's lifetime. One aim is to discover whether switching off the lubricin gene later in life will lead to arthritis-like symptoms.

"If lubricin is the first line of defense at the cartilage surface, then patients with rheumatoid arthritis might have an acquired deficiency of the protein," he says. "As they get older, their joints might have produced enzymes that degrade it, or their cells might not make enough." Therefore, therapeutic approaches that restore lubricin levels may be powerful adjuncts for helping persons with other forms of arthritis.

As straightforward as creating the mouse model of CACP proved, developing a mouse model of PPD has presented considerable challenges. When the scientists engineered mice to lack the culprit gene, called WISP3, surprisingly, the animals showed no signs of the disease. "We figured that one reason these mice might not show the same symptoms as people is that patients with PPD are out running around and playing, and the mice are living in a small cage with other mice," he says. "So, we tried giving them running wheels, to let them run as much as they want. Although our results are still preliminary, they suggest that activity may bring out joint disease in mice that lack WISP3. If this preliminary observation can be confirmed, then it suggests that WISP3 may function in cartilage to "remind" cartilage cells to maintain healthy joints after activities that can damage them.

"The Burroughs Wellcome Fund's support has been very important in that it enabled me not to have to rush into press with our early work on WISP3," Dr. Warman says. "We've had these mice for three years, and we've gone down a lot of false pathways in figuring out what the protein does. While otherwise we would have felt it necessary to publish the fact that these mice showed no symptoms, BWF's support enabled us to explore the biology in greater detail. And this further work led us to the exciting possibility that WISP3 helps joints respond to stress."

Most recently, Dr. Warman and his colleagues have made major strides in understanding yet another skeletal disease, acromesomelic dysplasia, Maroteaux type (AMDM). In identifying the gene underlying this inherited failure of bone growth, the researchers believe they might have hit upon a pathway for treating growth disorders in children.

"What's amazing about this particular condition is that growth after birth seems to be severely disrupted—much more so than growth before birth," Dr. Warman says. "So the pathway in which the AMDM gene participates differentially affects bone growth before and after we are born." The gene

underlying AMDM is a cellular receptor for a small bit of protein called a peptide. The simplicity of the peptide, he believes, might make it an alternative to other currently used growth factors, such as growth hormone, which is now approved for use in children with short stature. Moreover, the AMDM pathway might be helpful for persons with other disorders of skeletal growth, such as chrondroplasia.

Dr. Warman's fascination with the skeleton began in junior high, when he read an article about use of electric currents to heal intractable fractures. "This really got me interested in thinking about bone as a living tissue that could be affected by engineering," he recalls. "So, when I went to college, I thought I'd probably be a biomedical engineer." While he earned a Sc.B. in engineering from Brown University, Dr. Warman retained his interest in medicine, earning his M.D. from Cornell University. His love of children took him to a pediatric residency at Children's Hospital in Washington, D.C., and his continuing interest in genetics led to a fellowship in genetics at Children's Hospital in Boston. He strengthened his research credentials by taking research, clinical, and teaching posts at Harvard Medical School, before moving to Case.

"I've always enjoyed genetics, because I really enjoy helping people work through what are right now insoluble problems, for which we don't have any therapies," he says. "But I believe that one day we will be able to help a lot of our patients, and I want to be part of making that happen."

Report on Finance

At the end of our fiscal year, August 31, 2003, the Burroughs Wellcome Fund's investments totaled $587.0 million. BWF's primary financial goal is to pursue an investment strategy that will support annual spending needs and maintain a constant real level of assets over the long term. To achieve this goal, we place a high percentage of our investments in strategies that derive the bulk of their returns from exposure to U.S. and international capital markets. Hence, fluctuations in BWF's investment results will be due largely to variability in capital market returns.

BWF develops its investment policies with the recommendations and review of the Investment Committee, which is appointed by and reports to BWF's Board of Directors. The committee, which meets three times a year, has seven voting members, including four representatives from outside BWF and three representatives of our board. The board's chair, BWF's president, and BWF's vice president for finance also serve on the committee as nonvoting members.

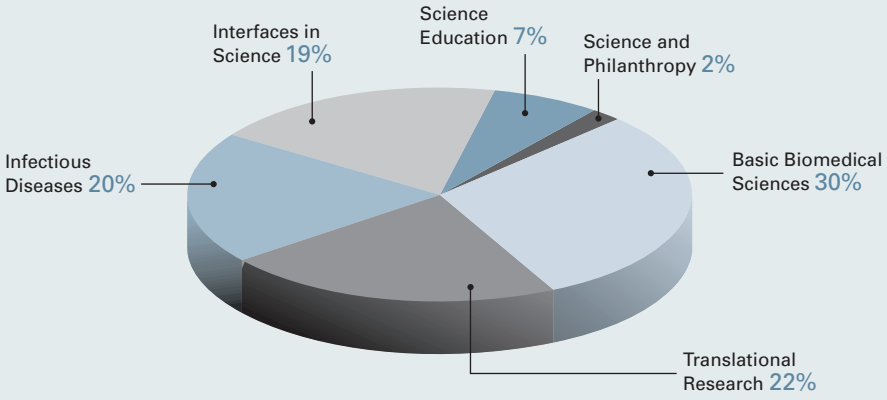
As part of BWF's investment strategy, we have established "allocation targets"—that is, percentages of our total assets to be invested in particular asset classes. Investment managers hired by BWF pursue more focused mandates within each sector. As of the end of the fiscal year, BWF's asset mix and market values were:

- U.S. large capitalization equity assets had a market value of $149.6 million. The sector's target allocation was 26 percent, and actual holdings stood at 25.5 percent.
- U.S. small capitalization equity assets had a market value of $92.5 million. The sector's target allocation was 19 percent, and actual holdings stood at 15.8 percent.
- International equity assets had a market value of $154.6 million. The sector's target allocation was 27 percent, and actual holdings stood at 26.3 percent.
- Fixed income assets had a market value of $119.9 million. The sector's target allocation was 25 percent, and actual holdings stood at 20.4 percent.
- Cash equivalent assets had a market value of $16.3 million. The sector's target allocation was 3 percent, and actual holdings stood at 2.8 percent.
- Alternative assets had a market value of $54.1 million. The sector did not have a target allocation, and actual holdings stood at 9.2 percent. The maximum permitted allocation to alternative assets stood at 14 percent.

The total market value of BWF's investments increased by $37.3 million, or 6.8 percent, from the end of the previous fiscal year. This increase in assets was due primarily to good returns in world equity markets from late March 2003 through the end of the fiscal year. BWF's total investment return for the fiscal year was 13.3 percent. Returns in all three equity sectors and the fixed income sector were positive for the fiscal year. The U.S. large capitalization equity sector returned +15.3 percent; the U.S. small capitalization equity sector had a +23.5 percent result; the international equity sector posted a return of +16.1 percent; and fixed income produced a +7.2 percent result.

As of August 31, 2003, BWF employed 10 investment managers. In the U.S. large capitalization equity sector, the managers were Independence Investment Associates, LSV Asset Management, and Cohen, Klingenstein and Marks. Credit Suisse Asset Management, Kennedy Capital Management, and M&I Investment Management managed U.S. small capitalization equities. Pacific Investment Management Company and Smith Breeden Associates were the fixed income managers. Capital Guardian Trust Company and Hansberger Global Investors managed international equities. BWF also held investments in seven venture capital funds: Intersouth Partners IV, V, and VI, the Spray Venture Fund, Mission Ventures II, the North Carolina Bioscience Investment Fund, and A. M. Pappas Life Science Ventures II. Finally, Quellos Capital Management managed a fund of absolute return strategies.

Grants Awarded



Report of Independent Auditors

To the Board of Directors of
The Burroughs Wellcome Fund

In our opinion, the accompanying statements of financial position and the related statements of activities and of cash flows present fairly, in all material respects, the financial position of The Burroughs Wellcome Fund (the "Fund") at August 31, 2003 and 2002, and the changes in its net assets and its cash flows for the years then ended in conformity with accounting principles generally accepted in the United States of America. These financial statements are the responsibility of the Fund's management; our responsibility is to express an opinion on these financial statements based on our audits. We conducted our audits of these statements in accordance with auditing standards generally accepted in the United States of America, which require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

Our 2003 audit was conducted for the purpose of forming an opinion on the basic financial statements taken as a whole. The information presented in Schedules I and II is presented for purposes of additional analysis and is not a required part of the basic financial statements. Such information has been subjected to the auditing procedures applied in the audit of the basic financial statements and, in our opinion, is fairly stated in all material respects in relation to the basic financial statements taken as a whole.

PricewaterhouseCoopers LLP

Raleigh, North Carolina
October 17, 2003

Statements of Financial Position

August 31, 2003 and 2002

(All dollar amounts presented in thousands)

	2003	2002
Assets		
Cash and cash equivalents	$27,587	$25,045
Marketable securities	549,712	538,392
Accrued interest and dividends receivable	2,139	2,134
Transactions receivable, net	7,964	-
Other assets	40	28
Total current assets	587,442	565,599
Property and equipment, net	13,230	13,870
Total assets	$600,672	$579,469
Liabilities and Net Assets		
Transactions payable, net	$ -	$15,459
Accounts payable and other liabilities	600	723
Deferred excise tax payable	498	-
Unpaid awards	64,566	70,940
Total liabilities	65,664	87,122
Unrestricted net assets	535,008	492,347
Total liabilities and net assets	$600,672	$579,469

The accompanying notes are an integral part of these financial statements.

Statements of Activities

Years Ended August 31, 2003 and 2002

(All dollar amounts presented in thousands)

	2003	2002
Revenues:		
Interest and dividends, less investment expenses of $2,767 and $3,289 in 2003 and 2002, respectively	$11,167	$12,879
Net realized (loss) gain on sales of marketable securities	(9,766)	(34,896)
Total revenues	1,401	(22,017)
Expenses:		
Program services	18,810	22,793
Management and general	4,269	4,564
Total expenses before net unrealized appreciation (depreciation) and federal excise tax	23,079	27,357
Net unrealized appreciation (depreciation) of marketable securities, net of provision for deferred federal excise taxes of $498 and $0 in 2003 and 2002, respectively	64,339	(34,763)
Change in net assets	42,661	(84,137)
Net assets at beginning of year	492,347	576,484
Net assets at end of year	$535,008	$492,347

The accompanying notes are an integral part of these financial statements.

Statements of Cash Flows

Years Ended August 31, 2003 and 2002

(All dollar amounts presented in thousands)

	2003	2002
Cash flows from operating activities:		
Change in net assets	$42,661	$(84,137)
Adjustments to reconcile change in net assets to net cash (used in) provided by operating activities:		
Depreciation	661	742
Net realized loss on sales of marketable securities	9,766	34,896
Net unrealized appreciation (depreciation) of marketable securities	(64,837)	34,763
Provision for deferred federal excise taxes	498	-
Awards granted, net of cancellations and change in unamortized discount	19,085	23,525
Award payments made	(25,458)	(31,473)
Changes in operating assets and liabilities:		
Accrued interest and dividends receivable	(5)	22
Federal excise tax receivable	-	1,403
Other assets	(12)	(6)
Transactions receivable, net	(7,964)	-
Transactions payable, net	(15,459)	(27,085)
Accounts payable and other liabilities	(123)	(237)
Net cash used in operating activities	(41,187)	(47,587)
Cash flows from investing activities:		
Purchases of marketable securities	(1,237,408)	(1,235,953)
Proceeds from sales of marketable securities	1,281,158	1,263,782
Purchase of property and equipment	(21)	(22)
Net cash provided by investing activities	43,729	27,807
Net (decrease) increase in cash and cash equivalents	2,542	(19,780)
Cash and cash equivalents at beginning of year	25,045	44,825
Cash and cash equivalents at end of year	$27,587	$25,045
Supplemental disclosure of cash flow information:		
Cash paid during the year for federal excise taxes	$ -	$ -

The accompanying notes are an integral part of these financial statements.

Years Ended August 31, 2003 and 2002

(All dollar amounts presented in thousands)

1. Organization and Summary of Significant Accounting Policies

The Burroughs Wellcome Fund (the "Fund") is a private foundation established to advance the medical sciences by supporting research and other scientific and educational activities.

Cash equivalents

Cash equivalents are short-term, highly liquid investments that are readily convertible to known amounts of cash and have a maturity of three months or less at the time of purchase.

Forward currency contracts

The Fund enters into financial instruments with off-balance sheet risk in the normal course of its investment activity; primarily forward contracts, to reduce the Fund's exposure to fluctuations in foreign currency exchange rates. These contracts are for delivery or sale of a specified amount of foreign currency at a fixed future date and a fixed exchange rate. Gains or losses on these contracts occur due to fluctuations in exchange rates between the commencement date and the settlement date. Gains and losses on settled contracts are included within "net realized gains or losses on sales of marketable securities," and the changes in market value of open contracts is included within "net unrealized appreciation (depreciation) of marketable securities" in the accompanying statements of activities. It is the Fund's policy to utilize forward contracts to reduce foreign exchange rate risk when foreign-based investment purchases or sales are anticipated.

The contract amount of these forward currency contracts totaled $8,021 and $14,132 at August 31, 2003 and 2002, respectively. Realized gains on forward currency contracts totaled $3 and $748 in 2003 and 2002, respectively. The market value of open forward currency contracts at August 31, 2003 and 2002 was $4 and $92, respectively. The market value is recorded as an asset in the Fund's financial statements. The average market value of open foreign currency contracts totaled $218 and $226 for the years ending August 31, 2003 and 2002, respectively.

Futures contracts

The Fund enters into futures contracts in the normal course of its investment activity to manage the exposure to interest rate risk associated with bonds and mortgage backed securities. The Fund is required to pledge collateral to enter into these contracts. The amounts pledged for futures contracts at August 31, 2003 and 2002 were $958 and $1,304, respectively. It is the Fund's intention to terminate these contracts prior to final settlement. Gains and losses on the contracts are settled on a daily basis. Included in transactions payable at August 31, 2003 and 2002 is the net settlement relating to these contracts of ($102) and ($120), respectively.

Options

The Fund utilizes options to manage the exposure to interest rate risk associated with mortgage backed securities. The market value of these options totaled ($8) and $1 at August 31, 2003 and 2002, respectively, which is recorded as an asset in the Fund's financial statements. The average fair value of open contracts totaled ($27) and $871 for the years ending August 31, 2003 and 2002. Realized losses on options totaled $131 and $732 for the years ending August 31, 2003 and 2002, respectively.

Marketable securities

Marketable securities are carried at estimated market values based on quoted prices. Gains and losses from sales of securities are determined on an average cost basis and are recognized when realized. Changes in the estimated market value of securities are reflected as unrealized appreciation or depreciation in the accompanying statements of activities. The Fund has investment advisors, which manage its portfolio of marketable securities. The Fund's management critically evaluates investment advisor performance and compliance with established diversification and investment policies.

Property and Equipment
Property and equipment is primarily comprised of a building, furniture, and computer equipment, which are stated at cost less accumulated depreciation and are being depreciated over their estimated useful lives using the straight-line method. Ordinary maintenance and repair costs are expensed as incurred.

Building	40 years
Furniture and Fixtures	7 years
Computer Equipment	3 years

Transactions Receivable and Transactions Payable, Net
These amounts represent the net receivable or payable resulting from investment transactions with trade dates prior to August 31 and settlement dates subsequent to August 31.

Awards Granted and Unpaid Awards
Grants are expensed at their fair value in the year in which the award is granted. Grants payable over several years are expensed, and carried on the statements of financial position, at the present value of their estimated future cash flows, using a risk free discount rate determined at the time the award is granted.

Functional Allocation of Expenses
Costs of Fund's operations and activities have been summarized on a functional basis in the statement of activities.

Estimated Fair Value of Financial Instruments
Financial instruments include cash and cash equivalents, marketable securities, accrued interest and dividends receivable, accounts payable, and unpaid awards. All financial instruments are reported at their estimated fair value. The carrying values of accrued interest and dividends receivable, accounts payable, and unpaid awards approximate fair values based upon the timing of future expected cash flows. The estimated fair value of marketable securities is determined based upon the latest quoted sales price for such securities as of the balance sheet date. The Fund's remaining assets and liabilities are not considered financial instruments.

Use of Estimates
The preparation of financial statements in conformity with generally accepted accounting principles requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates.

Market Risk
Market risk represents the risk of changes in value of a financial instrument, derivative or non-derivative, caused by fluctuations in interest rates, foreign exchange rates and equity prices. The Fund manages these risks by using derivative financial instruments in accordance with established policies and procedures.

2. Property and Equipment

The Fund's property and equipment consisted of the following:

	2003	2002
Building	$13,451	$13,451
Furniture and fixtures	1,735	1,735
Computer equipment	694	673
	15,880	15,859
Less: accumulated depreciation	(2,650)	(1,989)
	$13,230	$13,870

3. Federal Excise Taxes

The Fund is exempt from federal income taxes under Section 501(c)(3) of the Internal Revenue Code. However, since the Fund meets the definition of a private foundation under the Internal Revenue code, it is subject to federal excise tax on its annual net investment income.

Deferred federal excise taxes represent the tax liability on unrealized appreciation of marketable securities. At August 31, 2003, the Fund is in a net unrealized appreciation position, therefore, a deferred federal excise tax liability of $498 was recorded. At August 31, 2002, the Fund was in a net unrealized depreciation position, therefore, deferred federal excise taxes were not recorded.

4. Qualified Distributions

The Fund is required to distribute 5 percent of the excess of the aggregate fair market value of the assets over the acquisition indebtedness with respect to such assets. Failure to distribute according to Section 4942(e)(1) results in a tax equal to 15 percent of the undistributed income of the Fund.

5. Unpaid Awards

Unpaid awards as of August 31 are scheduled for payment as follows:

	2003	2002
Payable in less than one year	$24,660	$32,555
Payable in one to five years	41,329	40,404
	65,989	72,959
Unamortized discount	(1,423)	(2,019)
Total	$64,566	$70,940

The expected future liability to the Fund has been calculated based on discount rates ranging from 1.24 percent to 3.80 percent.

6. Marketable Securities

The cost and estimated market values of marketable securities at August 31 are as follows:

	2003		2002	
	Cost	Estimated Market Value	Cost	Estimated Market Value
U.S. and foreign governmental obligations	$64,792	$66,954	$74,419	$78,178
Corporate bonds	29,980	30,802	53,096	53,718
Common and preferred stocks	258,779	276,802	274,407	246,525
Foreign stocks and foreign equity funds	117,258	121,083	131,730	115,639
Option and forward foreign currency investments	(9)	(8)	83	93
Venture capital investments	16,798	11,930	13,834	12,283
Mutual fund	37,232	42,149	30,000	31,956
	$524,830	$549,712	$577,569	$538,392

7. Employee Benefit and Retirement Plans

The Fund provides medical insurance to all employees working at least thirty hours per week. Coverage extends to each employee's spouse and dependent children, if applicable. The expense for this employee benefit was $148 and $118 during fiscal 2003 and 2002, respectively.

The Fund has a defined-contribution retirement plan covering all employees working at least twenty hours per week. Under the terms of the plan, the Fund matches 50 percent of all employees' contributions up to 6 percent of the employee's annual compensation. Employees are 100 percent vested in employee and employer contributions immediately. The Fund also has a defined-contribution retirement plan funded solely through employer contributions. Under the terms of the plan, the Fund contributes 10 percent of the employee's annual compensation. This plan covers all employees and vesting in contributions is immediate. The expense for these retirement plans was $43 and $167 in fiscal 2003, and $42 and $162 in fiscal 2002, respectively.

8. Classification of Expenses

During the years ended August 31, expenses were classified as follows:

	2003		2002	
	Program Services	Management and General	Program Services	Management and General
Awards granted, net of cancellations and refunds of $4,191 and $7,833 in 2003 and 2002, respectively	$18,616	$ -	$22,793	$ -
Federal excise tax	-	122	-	-
Salaries and other employee expenses	93	2,188	-	2,236
Depreciation expense	-	661	-	743
Travel and entertainment	13	256	-	381
Maintenance and supplies	2	438	-	510
Honoraria	-	310	-	276
Professional fees	82	223	-	239
Printing and design costs	4	46	-	57
Miscellaneous	-	25	-	122
Total expenses	$18,810	$4,269	$22,793	$4,564

9. Related Parties

North Carolina Science, Mathematics, and Technology Education Center, Inc. ("SMT") was formed on April 24, 2002. The corporation solicits grants for the purpose of providing funding to improve the performance of students in science, mathematics, and technology.

The Fund granted $2,000 to SMT during the year ended August 31, 2003. In addition, the Fund paid $194,204 of expenses on behalf of SMT. Expenses included salaries, travel, entertainment, maintenance, supplies, professional fees, and printing cost.

The financial statements of the Fund and SMT are not presented on a consolidated basis, as the Fund is not the legal owner of SMT, does not have controlling interest of SMT's financial transactions, and does not have considerable representation on the board of SMT.

Schedule I:
Statement of Award Transactions

Year Ended August 31, 2003

(All dollar amounts presented in thousands)

Unpaid awards, beginning of year	$70,940
Add – Awards granted (Schedule II)	22,211
Net increase in unamortized discount	596
Less – Award payments made	(25,458)
Award cancellations (excluding refunds)	(3,723)
Unpaid awards, end of year	$64,566

Schedule II:
Statement of Awards Granted

Year Ended August 31, 2003

Schedule II information is included in the "Grants Index" beginning on the opposite page. The dollar amounts listed in the schedule reflect the actual dollar amounts (not rounded to thousands) approved and paid to awardees.

Program Summary

	Approved	Paid	Transferred/ Cancelled*
Basic Biomedical Sciences			
Career Awards in the Biomedical Sciences	$7,756,053	$9,025,466	$2,129,500
Career Awards Collaborative Grant	-	8,400	-
Fellowships in the Life Sciences	-	123,000	-
Fellowships in Obsetrics and Gynecology	-	51,000	-
Hitchings-Elion Fellowships	422,833	519,333	518,625
Reproductive Science	20,000	193,000	36,000
Other Grants	27,500	25,150	-
Total	$8,226,386	$9,945,349	$2,684,125
Infectious Diseases			
Investigators in Pathogenesis of Infectious Disease	$3,200,000	$720,000	$ -
New Initiatives in Malaria Research	-	675,000	-
New Investigator Awards in Molecular Parasitology	-	315,000	-
New Investigator Awards in Molecular Pathogenic Mycology	-	315,000	-
Scholar Awards in Molecular Parasitology	-	795,000	-
Scholar Awards in Molecular Pathogenic Mycology	-	662,500	-
Other Grants	478,500	1,160,632	-
Total	$3,678,500	$4,643,132	$ -
Interfaces in Science			
Career Awards at the Scientific Interface	$3,564,000	$1,157,600	$ 64,000
Functional Genomics Innovation Awards	-	678,251	-
Institutional Awards at the Scientific Interface	-	827,738	-
Other Grants	68,000	68,000	-
Total	$3,632,000	$2,731,589	$ 64,000
Science Education			
Student Science Enrichment Program	$899,411	$682,873	$ -
Other Grants	358,500	298,930	-
Total	$1,257,911	$981,803	$ -

	Approved	Paid	Transferred/ Cancelled*
Science and Philanthropy			
Communications/Science Writing	36,000	36,000	$ -
General Philanthropy	$67,550	$67,550	-
Science Policy	175,000	75,000	-
Special Award	1,500	1,500	-
Total	$280,050	$180,050	$ -
Translational Research			
Clinical Scientist Awards in Translational Research	$5,051,612	$5,876,612	$ 975,000
New Investigator Awards in the Basic Pharmacological Sciences	-	560,000	-
New Investigator Awards in the Toxicological Sciences	-	455,000	-
Other Grants	85,000	85,000	-
Total	$5,136,612	$6,976,612	$ 975,000
Totals	**$22,211,459**	**$25,458,535**	**$3,723,125**

Grand Totals† { Approved: $22,211,459 Paid: $25,458,535

* The "Transferred/Cancelled" totals reflect grants made to award recipients who changed institutions, modified the terms of their grant at their current institution, or both changed institutions and modified their grant. In these cases, BWF's policy has been to cancel the remaining portion of the original grant and, as necessary, approve a new grant. When the award recipient has changed institutions, the new grant is made to the new institution; when the award recipient has not moved but has modified the terms, the new grant is made to the current institution.

† To more accurately reflect the total amount that BWF approved in actual "new" dollars during this fiscal year, the "Transferred/Cancelled" total must be deducted from the "Approved" total.

Key to Grants Index—BWF makes all grants to nonprofit organizations. For most of the programs listed in the following sections, the name of the individual on whose behalf the grant is made is listed first, the title of the award recipient's project is listed second, and the name of the organization that received the money is listed third. For programs that may have coaward recipients, the award recipients and their organizations are listed first, followed by the project title. For grants made directly to organizations and not on behalf of an individual, the name of the organization is listed first, followed by the title of the project or a brief description of the activity being supported.

Totals { Approved: $8,226,386
Paid: $9,945,349
Transferred/Cancelled: $2,684,125

Career Awards in the Biomedical Sciences

Career awards are postdoctoral-faculty bridging awards. During the fiscal year, some award recipients change institutions, modify the terms of their award at their current institution, or both change institutions and modify their award. In these cases, BWF's policy has been to cancel the remaining portion of the original award and, as necessary, approve a new award. When the award recipient has changed institutions, the new award is made to the new institution; when the award recipient has not moved but has modified the terms, the new award is made to the current institution. In the following descriptions, the name of the award recipient is listed first, the title of the project is listed second, the award recipient's current institution is listed third, and the amount approved or paid to the institution is listed fourth. For award recipients who either changed institutions or modified their award, the portion of the award paid to the original institution, as well as any portion that was transferred or cancelled, is listed last, in parentheses. For new award recipients still in the postdoctoral period, the portion of the award intended to cover a future faculty appointment is listed last, in parentheses.

Suzanne J. Admiraal, Ph.D.
Biosynthesis of hybrid natural products
Harvard Medical School
Paid $58,000

Matthew L. Albert, M.D., Ph.D.
Tumor immunity versus tumor-mediated immunosuppression: characterizing the cellular and molecular mechanism of cross-priming and cross-tolerance
Rockefeller University
Paid $31,500

Ravi Allada, M.D.
Molecular and genetic analysis of the circadian rhythm gene, Clock, in *Drosophila*
Northwestern University
Paid $65,500

Matthew P. Anderson, M.D., Ph.D.
Role of T-type calcium channels in thalamic and hippocampal rhythmic activity
Harvard Medical School
Paid $65,000 (to Beth Israel Deaconess Medical Center)
($44,000 of original award for a future faculty appointment was transferred/cancelled; $44,000 was approved and paid to the Massachusetts Institute of Technology)

Kaveh Ashrafi, Ph.D.
Comprehensive analysis of regulatory mechanisms of fat biology
University of California-San Francisco School of Medicine
Approved $500,000 Paid $50,000

Vahe Bandarian, Ph.D.
Biosynthesis of deazapurine secondary metabolites
University of Arizona
Approved $58,000 Paid $54,000
($29,000 of the original award to the University of Michigan-Ann Arbor was paid; $58,000 of original award to the University of Michigan-Ann Arbor was transferred/cancelled)

Jody L. Baron, M.D., Ph.D.
Role of the innate immune system in acute and chronic hepatitis B: studies in a novel transgenic mouse model of primary HBV infection
University of California-San Francisco School of Medicine
Paid $65,500

Greg J. Bashaw, Ph.D.
Molecular mechanisms of attractive and repulsive axon guidance at the midline of *Drosophila*
University of Pennsylvania Medical Center
Paid $127,500

Aaron P. Batista, Ph.D.
Neural gating within the cerebral cortex during sensory-motor behavior
Stanford University School of Medicine
Approved $116,000 Paid $29,000
($384,000 approved for future faculty appointment)

Leonardo Belluscio, Ph.D.
Learning and memory in the mouse olfactory bulb
($386,000 of the original award for a future faculty appointment was transferred/cancelled)

Guoqiang Bi, Ph.D.
Spatio-temporal specificity of synaptic plasticity at single synaptic contacts
University of Pittsburgh School of Medicine
Paid $131,000

David Bilder, Ph.D.
Genetic analysis of epithelial cell architecture
University of California-Berkeley
Approved $10,760 Paid $189,500
($29,500 of the original award to Harvard Medical School was transferred/cancelled)

Cornelius F. Boerkoel, M.D., Ph.D.
Drosophila model for dissection SMARCAL1 function
Baylor College of Medicine
Paid $93,000

Azad Bonni, M.D., Ph.D.
Regulation of glial fate specification in the central nervous system
Harvard Medical School
Paid $65,500
($29,500 of the original award to Harvard Medical School was transferred/cancelled)

Carrie B. Brachmann, Ph.D.
Using *Drosophila* as a tool for the study of apoptotic regulation
University of California-Irvine
Paid $131,000
($31,500 of the original award to Washington University School of Medicine was transferred/cancelled)

Edward S. Brodkin, M.D.
Genetic analysis of anxiety-related behaviors in mice
University of Pennsylvania School of Medicine
Paid $131,487

Chester W. Brown, M.D., Ph.D.
Understanding the reproductive roles of the activins using an activin beta B knock-in model
Baylor College of Medicine
Paid $127,500

Richard K. Bruick, Ph.D.
Investigation of hypoxia sensing and signaling pathways
University of Texas Southwestern Medical Center-Dallas
Paid $84,250

Walter R. Burack, M.D., Ph.D.
Analysis of the immunological synapse: a membrane-associated machine
($386,000 of the original award for future faculty appointment has been transferred/cancelled)

Kathleen M. Caron, Ph.D.
Reproductive and cardiovascular effects of the adrenomedullin system
University of North Carolina-Chapel Hill School of Medicine
Paid $97,000

David C. Chan, M.D., Ph.D.
Structural and mechanistic studies of virus-mediated membrane fusion
California Institute of Technology
Paid $60,500

Thomas R. Clandinin, Ph.D.
Dissecting neuronal target selection in the *Drosophila* visual system
Stanford University School of Medicine
Paid $127,500

Michael K. Cooper, M.D.
Modulation of sonic hedgehog signal transduction by cholesterol homeostasis
Vanderbilt University Medical Center
Approved $402,678 Paid $193,000
($33,000 of the original award to Johns Hopkins University School of Medicine was paid; $386,000 of the original award to Johns Hopkins University School of Medicine was transferred/cancelled)

John D. Crispino, Ph.D.
Functional characterization of hematopoietic transcription factor complexes
University of Chicago
Paid $65,500

Paul De Koninck, Ph.D.
Decoding rhythms in the nervous system
Laval University
Paid $127,500

Abby F. Dernburg, Ph.D.
Chromosome architecture and the fidelity of meiotic segregation
University of California-Berkeley
Paid $127,500

Ricardo E. Dolmetsch, Ph.D.
Voltage-gated calcium channel signaling to the nucleus
Stanford University School of Medicine
Paid $65,500
($31,500 of the original award to Harvard Medical School was paid)

Kelly S. Doran, Ph.D.
Penetration of the blood-brain barrier in GBS meningitis
University of California-San Diego
Paid $193,000

Charles G. Eberhart, M.D., Ph.D.
Analysis of medulloblastoma pathobiology and response to novel therapies using murine transgenic models
Johns Hopkins University School of Medicine
Paid $131,000

Peter J. Espenshade, Ph.D.
Molecular mechanism of cholesterol homeostasis in mammalian cells
Johns Hopkins University School of Medicine
Paid $131,000
($31,500 of the original award to the University of Texas Southwestern Medical Center-Dallas was transferred/cancelled)

Miguel Estevez, M.D., Ph.D.
Investigation of a calcium channel related to migraine and epilepsy in both an invertebrate and a mouse model
University of Pittsburgh Medical Center
Paid $31,500

Kathryn M. Ferguson, Ph.D.
Structural basis for erbB receptor activation by epidermal growth factor (EGF) agonists and neuregulin
University of Pennsylvania School of Medicine
Paid $65,500
($31,500 of the original award to the University of Pennsylvania School of Medicine was transferred/cancelled)

Elizabeth A. Finch, Ph.D.
Postsynaptic calcium signaling by inositol trisphosphate in neuronal dendrites
Emory University School of Medicine
Paid $65,500

Nicholas R. Gaiano, Ph.D.
Neural stem cells in the mammalian forebrain: the roles of Notch and FGF signaling
Johns Hopkins University School of Medicine
Approved $23,307 Paid $193,000

Timothy P. Galitski, Ph.D.
Genetic networks
Institute for Systems Biology
Paid $124,000
($31,500 of the original award to Massachusetts Institute of Technology was transferred/cancelled)

Erin C. Gaynor, Ph.D.
Molecular basis of colonization and invasion in the foodborne enteric pathogen *Campylobacter jejuni*
Stanford University School of Medicine
Paid $29,000

Jeffrey S. Glenn, M.D., Ph.D.
Prenylation and viral assembly
Stanford University School of Medicine
Paid $60,500

Joseph A. Gogos, M.D., Ph.D.
Genetic analysis of connectivity in the mammalian olfactory system
Columbia University College of Physicians and Surgeons
Paid $118,250

Joshua I. Gold, Ph.D.
Neural basis of perceptual-decision formation
University of Pennsylvania School of Medicine
Paid $65,500

Or P. Gozani, M.D., Ph.D.
Regulation of chromatin remodeling events by nuclear phosphoinositides
Harvard Medical School
Approved $58,000 Paid $29,000
($442,000 approved for future faculty appointment)

Michael Graziano, Ph.D.
From eye to hand: sensory-motor integration in the primate brain
Princeton University
Paid $127,500

Jay T. Groves, Ph.D.
Studies of cell recognition and signaling with micropatterned lipid membranes
University of California-Berkeley
Paid $127,500

Karen J. Guillemin, Ph.D.
Genetic and cellular basis of *Helicobacter pylori*-associated malignancies
University of Oregon
Paid $127,500

Victoria G. Herman, Ph.D.
Defining the molecular code for synaptic target selection
University of California-Los Angeles School of Medicine
Paid $31,500

Joel N. Hirschhorn, M.D., Ph.D.
Genetic analysis of complex endocrine disorders
Harvard Medical School
Paid $124,000

Michael D. Hogarty, M.D.
BIN1: a *MYCN* interacting neuroblastoma suppressor
University of Pennsylvania School of Medicine
Paid $127,500

Lora V. Hooper, Ph.D.
Molecular analysis of commensal host-microbial interactions in the intestine
University of Texas Southwestern Medical Center-Dallas
Paid $65,500

Jennifer S. Hovis, Ph.D.
Understanding lipid and protein interactions at the molecular level in model cell membranes
Purdue University
Paid $193,000

Christina M. Hull, Ph.D.
Cell identity, sexual development, and virulence in the human fungal pathogen *Cryptococcus neoformans*
University of Wisconsin Medical School
Approved $500,000 Paid $50,000

Akiko Iwasaki, Ph.D.
Defining the mechanism of immune induction and effector function in the female genital mucosa
Yale University School of Medicine
Paid $65,500

Raymond H. Jacobson, Ph.D.
TBP-related factor and selectivity factor I: probing TBP function in alternative contexts
University of Texas M. D. Anderson Cancer Center
Paid $118,250

Ursula H. Jakob, Ph.D.
Structural and functional characterization of new heat shock proteins
University of Michigan-Ann Arbor
Paid $62,000

James D. Jontes, Ph.D.
Role of protocadherins in neural development studied in living zebrafish embryos
Stanford University
Paid $64,250

Susan M. Kaech, Ph.D.
Investigation of the mechanisms that regulate memory CD8 T cell development
Emory University School of Medicine
Approved $58,000 Paid $29,000
($442,000 approved for future faculty appointment)

Dennis H. Kim, M.D., Ph.D.
Genetic analysis of innate immunity in *Caenorhabditis elegans*
Harvard Medical School (paid General Hospital Corporation)
Approved $58,000 Paid $29,000
($442,000 approved for future faculty appointments)

Suzanne L. Kirby, M.D., Ph.D.
Proliferative advantage for therapeutic bone marrow
University of North Carolina-Chapel Hill School of Medicine
Approved $6,593 Paid $6,593

Laura J. Knoll, Ph.D.
Molecular genetic approaches to investigate developmental regulation in *Toxoplasma gondii*
University of Wisconsin-Madison
Approved $2,885 Paid $64,885

William R. Kobertz, Ph.D.
Molecular interactions of the lipid-exposed surfaces of integral membrane proteins
University of Massachusetts Medical School
Paid $193,000

Benhur Lee, M.D.
HIV-1 coreceptors and their role in HIV-associated hematopoietic dysfunction
University of California-Los Angeles School of Medicine
Paid $131,000

Brian C. Lewis, Ph.D.
Modeling tumor initiation, progression, and metastasis using tissue-specific somatic gene transfer
Weill Medical College of Cornell University
Paid $29,000

Jeh-Ping Liu, Ph.D.
Molecular mechanisms in neural crest specification
University of Virginia Health System
Paid $121,000

Minmin Luo, Ph.D.
Integration of pheromonal signals and hormonal cues in mammalian reproduction
Duke University Medical Center
Paid $29,000

Mala S. Mahendroo, Ph.D.
Characterization of fecundity and parturition defects in mice deficient in steroid 5 alpha-reductase type 1
University of Texas Southwestern Medical Center-Dallas
Paid $31,350

Anna K. Majewska, Ph.D.
Imaging rapid plasticity in the visual cortex
Massachusetts Institute of Technology
Approved $58,000 Paid $29,000
($442,000 approved for future faculty appointment)

Margaret E. McLaughlin, M.D.
Effects of heterotypic cell interactions and blood-borne signals on tumors of the nervous system
Massachusetts Institute of Technology
Paid $58,000

James M. Olson, M.D., Ph.D.
NeuroD abrogation in neuroblastoma
University of Washington School of Medicine
Paid $121,000

Catherine L. Peichel, Ph.D.
Genetic and molecular basis of reproductive isolation of threespine sticklebacks
Fred Hutchinson Cancer Research Center
Approved $58,000 Paid $64,000
($58,000 of the original award to Stanford University School of Medicine was transferred/cancelled)

Thomas T. Perkins, Ph.D.
Measurements of single DNA-based molecular motors
University of Colorado-Boulder
Paid $124,000

Samuel J. Pleasure, M.D., Ph.D.
Molecular control of cell fate in the dentate gyrus
University of California-San Francisco School of Medicine
Paid $65,500

Martin R. Pollak, M.D.
Mouse molecular genetic studies of the extracellular Ca^{2}+-sensing receptor
Harvard Medical School
Paid $60,500

Matthew H. Porteus, M.D., Ph.D.
Regulation of gene targeting in vertebrate somatic cells
University of Texas Southwestern Medical Center-Dallas
Paid $55,250
($29,000 of the original award to California Institute of Technology was paid)

Salman T. Qureshi, M.D.
Genetic analysis of innate resistance to bacterial pathogens
McGill University Faculty of Medicine
Approved $357,500 Paid $60,500
($357,500 of the original award to Yale University School of Medicine was transferred/cancelled)

David E. Reich, Ph.D.
Applying population genetics to find genes for common diseases
Harvard Medical School
Approved $500,000 Paid $50,000

Douglas N. Robinson, Ph.D.
Studies of the mechanisms of cytokinesis using *Dictyostelium*
Johns Hopkins University School of Medicine
Paid $127,500
($31,500 of the original award to Stanford University School of Medicine was transferred/cancelled)

Aimee K. Ryan, Ph.D.
Analysis of inductive events responsible for specification and differentiation of the anterior pituitary gland
McGill University
Paid $121,000

Bernardo L. Sabatini, M.D., Ph.D.
Role of localized biochemical signaling in the regulation of synaptic function and spine morphogenesis
Harvard Medical School
Paid $124,000
($29,500 of the original award to Cold Spring Harbor Laboratory was transferred/cancelled)

Stephen W. Santoro, Ph.D.
Directed evolution of natural and unnatural proteins and oligomers for gene manipulation, drug discovery, and biochemical investigation
Harvard University
Approved $116,000 Paid $58,000
($29,000 of the original award to Scripps Research Institute was transferred/cancelled; $29,000 of the original award to Scripps Research Institute was paid)
($87,000 of the original award for future faculty appointment was transferred/cancelled)
($9,287 approved for future faculty appointment)

Erica O. Saphire, Ph.D.
Structural studies of *Ebola* viral pathogenesis
Scripps Research Institute
Approved $500,000 Paid $29,000

Bradley L. Schlaggar, M.D., Ph.D.
Development of cognition: fMRI studies
Washington University School of Medicine
Paid $84,250

Maria A. Schumacher, Ph.D.
Structural biology of cell growth, development, and regulation
Oregon Health and Science University
Paid $193,000

Kristin E. Scott, Ph.D.
Taste representation in *Drosophila* brain
University of California-Berkeley
Paid $84,250
($29,000 of the original award to Columbia University College of Physicians and Surgeons was transferred/cancelled)

Shu-ou Shan, Ph.D.
Mechanism of signal recognition particle-mediated protein targeting
University of California-San Francisco School of Medicine
Approved $116,000 Paid $29,000
($384,000 approved for future faculty appointment)

Krishna V. Shenoy, Ph.D.
Early reach plans in posterior parietal cortex
Stanford University
Paid $127,500

Donald C. Sheppard, M.D.
Isolation and characterization of genes involved in morphogenesis and virulence of *Aspergillus fumigatus*
University of California-Los Angeles School of Medicine
Paid $87,000

Elaine K. Sia, Ph.D.
Analysis of yeast mutants with altered simple repeat stability
University of Rochester
Paid $34,637

Douglas E. Smith, Ph.D.
Single molecular studies of viral DNA packaging
University of California-San Diego
Paid $127,500

Theodore S. Steiner, M.D.
Isolation and characterization of an interleukin 8 releasing protein from enteroaggregative *Escherichia coli*
University of British Columbia Faculty of Medicine
Approved $12,669 Paid $131,000

Collin M. Stultz, M.D., Ph.D.
Conformational free energy landscape of collagen and its relationship to atherosclerotic plaque rupture
Harvard Medical School (paid Brigham and Women's Hospital)
Approved $58,000
($442,000 approved for future faculty appointment)

Xin Sun, Ph.D.
Understanding the endoderm in organogenesis and regeneration
University of Wisconsin Medical School
Paid $193,000

Surachai Supattapone, M.D., D.Phil.
Structure and biology of a soluble prion
Dartmouth Medical School
Paid $118,250

Roger B. Sutton, Ph.D.
Biophysical and structural investigation of Ca^{+2} in neurotransmitter release
University of Texas Medical Branch-Galveston
Approved $36,824 Paid $124,000

Susanne J. Szabo, Ph.D.
T-bet, a novel t-box transcription factor that directs T-helper cell type 1 lineage commitment
Harvard School of Public Health
Approved $63,000 Paid $63,000
($63,000 of the original award for a future faculty appointment was transferred/cancelled)

Sarah A. Tishkoff, Ph.D.
Molecular sequence variation in G6PD and its role in malarial resistance
University of Maryland-College Park
Paid $60,500

Heidi A. Tissenbaum, Ph.D.
Genetic and molecular analysis of genes controlling longevity in *Caenorhabditis elegans*
University of Massachusetts Medical School
Paid $127,500

Stephen H. Tsang, M.D., Ph.D.
Unraveling genetic pathways leading to cell death in mice lacking the gamma subunit of the cGMP phosphodiesterase
University of California-Los Angeles School of Medicine
Paid $31,500

Kevin B. Urdahl, M.D., Ph.D.
Role of MHC class I molecules against tuberculosis
University of Washington School of Medicine
Approved $116,000 Paid $29,000
($384,000 approved for future faculty appointment)

Amy J. Wagers, Ph.D.
Dynamic circulation of hematopoietic stem cells: implications for stem cell function
Stanford University School of Medicine
Approved $58,000 Paid $29,000
($442,000 approved for future faculty appointment)

John B. Wallingford, Ph.D.
Molecular control of cell motility during vertebrate gastrulation
University of California-Berkeley
Paid $58,000

Michael M. Wang, M.D., Ph.D.
Estrogen receptors and neuroprotection against excitotoxic injury
Johns Hopkins University School of Medicine
Paid $65,500

Anthony P. West, Ph.D.
Identification of the natural ligand of Methuselah, a *Drosophila* GPCR associated with extended lifespan
California Institute of Technology
Paid $64,250

Carmen J. Williams, M.D., Ph.D.
Signal transduction mechanisms during mouse egg activation
University of Pennsylvania School of Medicine
Paid $60,500

Michael B. Yaffe, M.D., Ph.D.
Scaffolding and chaperone proteins in signal transduction: 14-3-3 regulation of mitosis and programmed cell death
Massachusetts Institute of Technology
Paid $65,500

Deborah L. Yelon, Ph.D.
Patterning during organogenesis: genetic analysis of cardiac chamber formation
New York University School of Medicine
Paid $65,500

Jennifer A. Zallen, Ph.D.
Molecular analysis of dynamic cell rearrangements in *Drosophila*
Princeton University
Paid $29,000

Yanping Zhang, Ph.D.
ARF-MDM-p53 tumor suppression pathway
University of Texas M. D. Anderson Cancer Center
Approved $12,313 Paid $65,500

Karen M. Zito, Ph.D.
Regulation of synapse formation in the mammalian cortex
Cold Spring Harbor Laboratory
Paid $29,000

Subtotals
Approved: $7,756,053
Paid: $9,025,466
Transferred/Cancelled: $2,129,500

Career Awards Collaborative Grant

Konstantin V. Severinov, Ph.D.
Two sessions for the 2003 FASEB summer conference on transcription in prokaryotes
Rutgers, the State University of New Jersey-New Brunswick
Paid $8,400

Subtotal { **Paid: $8,400**

Fellowships in the Life Sciences

Diane McFadden, Ph.D.
Characterization of *O*-acetylated carbohydrate epitopes on *Cryptococcus neoformans*
Albert Einstein College of Medicine
Paid $41,000

Scott T. R. Walsh, Ph.D.
Molecular recognition studies of human placental lactogen
University of Chicago
Paid $41,000

Robert T. Wheeler, Ph.D.
Creating a diversity of cell surface adhesin molecules in fungal pathogenesis
Whitehead Institute for Biomedical Research
Paid $41,000

Subtotal { **Paid: $123,000**

Fellowships in Obstetrics and Gynecology

Angeles Aleida Alvarez, M.D.
Regulation of angiogenesis in ovarian cancer and development of anti-angiogenesis therapy
Duke University Medical Center
Paid $51,000

Subtotal { **Paid: $51,000**

Hitchings-Elion Fellowships

Catherine J. Baty, D.V.M., Ph.D.
Feline familial hypertrophic cardiomyopathy: a natural model of human familial hypertrophic cardiomyopathy
University of Pittsburgh School of Medicine
Approved $24,500 Paid $24,500
($24,500 of the original award to the Medical University of South Carolina College of Medicine was transferred/cancelled)

Michael W. Black, Ph.D.
Secretion-dependent regulation of ribosome synthesis in *Saccharomyces cerevisiae*
California Polytechnic State University
Paid $84,000

John W. R. Copeland, Ph.D.
Activation of SRF actin remodelling proteins
Imperial Cancer Research Fund
Paid $30,000

Aaron R. Dinner, Ph.D.
Molecular mechanism of free radical oxidative DNA damage
University of Chicago
Paid $38,750
($60,125 of the original award for future faculty appointment was transferred/cancelled)
($4,625 to the University of California-Berkeley was approved and paid)

Daniel Durocher, Ph.D.
Role of FHA domains during DNA damage signaling
University of Toronto
Paid $38,750

Francine Durocher, Ph.D.
Identifying common low penetrance genes and gene-environment interactions in breast cancer
Laval University
Approved $8,708 Paid $8,708

Reuben S. Harris, Ph.D.
Delineation of the mechanisms of immunoglobulin gene hypermutation
University of Minnesota-Twin Cities
Approved $168,000
($168,000 of the original award to the Medical Research Council was transferred/cancelled)

Alan J. Herr, Ph.D.
Probing the pathway of RNA mediated defense with viral suppressor genes
Sainsbury Laboratory
Paid $27,750

Kenro Kusumi, Ph.D.
Notch pathway patterning of the mammalian brain and skeleton
University of Pennsylvania School of Medicine
Paid $90,500

Jacqueline L. S. Milne, Ph.D.
($49,000 of the original award to the Medical Research Council Laboratory of Molecular Biology was transferred/cancelled)

Stephen C. Ogg, Ph.D.
($49,000 of the original award to the University of Dundee was transferred/cancelled)

Jonathan K. Pritchard, Ph.D.
Population structure and linkage disequilibrium in association mapping
University of Chicago
Paid $38,750

David J. Rossi, Ph.D.
Mechanisms of ischemia-induced excitotoxicity
Oregon Health and Science University
Approved $168,000 Paid $84,000
($168,000 of the original award to University College London was transferred/cancelled)

Michael E. Zuber, Ph.D.
Molecular and cellular interactions required for vertebrate eye field formation
State University of New York Upstate Medical University
Approved $49,000 Paid $49,000

Subtotals
Approved: $422,833
Paid: $519,333
Transferred/Cancelled: $518,625

Reproductive Science

Marine Biological Laboratory
Support for the Frontiers in Reproduction course
Paid $56,125
($36,000 of the original award was transferred/cancelled)

Society for Gynecologic Investigation
Support for student and postdoctoral travel fellowships to attend the annual meeting in Houston, Texas, in March 2004, as well as support for the Trainee Forum; directed by BWF Board Member Dr. Jerry Strauss
Approved $20,000 Paid $20,000

University of California-San Francisco School of Medicine
Support for the Reproductive Scientist Development Program
Paid $80,000

University of Pennsylvania School of Medicine
Support for the Frontiers in Reproduction Course
Paid $36,875

Subtotals
Approved: $20,000
Paid: $193,000
Transferred/Cancelled: $36,000

Other Grants

In addition to making competitive awards, BWF makes non-competitive grants for activities that are closely related to our major focus areas. These grants are intended to enhance the general environment for research in the targeted areas.

American Association for the Advancement of Science
Support for *Science's* Next Wave career development program on interviewing skills
Approved $2,750

American Society for Cell Biology
Support for the society's annual meeting
Paid $400

American Society for Cell Biology
Support for postdoctoral travel awards to the 43rd American Society for Cell Biology annual meeting
Approved $2,500 Paid $2,500

Commission on Professionals in Science and Technology
Support for operating expenses
Approved $500 Paid $500

Lindau Nobel Prize Winners Foundation
Support for travel to the Lindau Nobel prize winners meeting for three BWF grant recipients
Approved $7,500 Paid $7,500

National Academies
Support for publication and dissemination of the *Guide to Recruiting and Advancing Women Scientists and Engineers in Academia*
Approved $4,000 Paid $4,000

National Academies
Support for the project on recruiting and advancing women in science and engineering
Approved $4,000 Paid $4,000

National Institute of Environmental Health Sciences Conditional Gift Fund
Support for the 2003 Biomedical Science and Career Fair
Approved $250 Paid $250

Society for Neuroscience
Support for postdoctoral fellows to attend the 2003 Society for Neuroscience annual meeting
Approved $5,000 Paid $5,000

University of North Carolina-Chapel Hill School of Medicine
Support for a symposium to introduce postdoctoral fellows and junior faculty to management techniques
Approved $1,000 Paid $1,000

Subtotals { **Approved: $27,500** / **Paid: $25,150**

Totals { Approved: $3,678,500
Paid: $4,643,132

Investigators in Pathogenesis of Infectious Disease

David C. Bloom, Ph.D.
Identification of neuron-specific factors that regulate HSV-1 chromatin structure and transcription during latency
University of Florida College of Medicine
Approved $400,000

Barbara A. Burleigh, Ph.D.
Functional characterization of the role of the host cell fibrogenic response in *Trypanosoma cruzi* infection
Harvard School of Public Health
Paid $80,000

Zhijian J. Chen, Ph.D.
Role of TRAF5-regulated IKK activators in innate immunity
University of Texas Southwestern Medical Center-Dallas
Paid $80,000

Dana A. Davis, Ph.D.
Control of phenotypic switching and pathogenesis by the Mds3 protein
University of Minnesota-Twin Cities
Approved $400,000

Maurizio Del Poeta, M.D.
Role of inositol phosphoryl ceramide synthase 1 (IPC1) in fungal-host interaction
Medical University of South Carolina College of Medicine
Paid $80,000

David A. Fidock, Ph.D.
Role of *Plasmodium falciparum* transmembrane proteins in parasite susceptibility to heme-binding antimalarials
Albert Einstein College of Medicine of Yeshiva University
Approved $400,000

Michael J. Gale Jr., Ph.D.
Control of hepatitis C virus replication
University of Texas Southwestern Medical Center-Dallas
Approved $400,000

Heidi Goodrich-Blair, Ph.D.
Pathogenesis of *Xenorhabdus nematophilus* in insects: a model for the innate immune response to bacterial pathogens
University of Wisconsin-Madison
Paid $80,000

David B. Haslam, M.D.
Mechanisms of *Shiga* toxin translocation and intoxication within host cells
Washington University School of Medicine
Paid $80,000

Margarethe J. Kuehn, Ph.D.
Toxin trafficking via vesicles
Duke University Medical Center
Paid $80,000

Andrew S. Neish, M.D.
Transgenic analysis of prokaryotic effector proteins in the eukaryote *Drosophila melanogaster*
Emory University School of Medicine
Approved $400,000

Eric J. Rubin, M.D., Ph.D.
Cell signaling by bacterial cytokines in *Mycobacterium tuberculosis*
Harvard School of Public Health
Approved $400,000

C. Erec Stebbins, Ph.D.
Structural studies of bacterial virulence factors
Rockefeller University
Paid $80,000

Ren Sun, Ph.D.
Identification of cellular factors that determine the fate of herpes virus infection: latency versus lytic replication
University of California-Los Angeles School of Medicine
Paid $80,000

Chloe L. Thio, M.D.
Identification of human genes associated with hepatitis B virus outcomes
Johns Hopkins University School of Medicine
Paid $80,000

Wenqing Xu, Ph.D.
Innate immunity: how do toll-like receptors recognize microbial pathogens?
University of Washington School of Medicine
Approved $400,000

Thomas C. Zahrt, Ph.D.
Mycobacterium tuberculosis regulators modulating reactivation
Medical College of Wisconsin
Approved $400,000

Subtotals { **Approved: $3,200,000** / **Paid: $720,000**

New Initiatives in Malaria Research Awards

Russ B. Altman, M.D., Ph.D.
Stanford University School of Medicine
Knowledge base of biological function for malaria
Paid $50,000

Scott D. Bohle, Ph.D.
McGill University
Peter W. Stephens, Ph.D.
State University of New York-Stony Brook
Interaction of the quinoline antimalarials and malaria pigment
Paid $150,000 (McGill University)

Fred E. Cohen M.D., D.Phil.
University of California-San Francisco
Joseph L. DeRisi, Ph.D.
University of California-San Francisco School of Medicine
Functional genomics approach to identification of new antimalarial drug targets
Paid $100,000

David A. Fidock, Ph.D.
William R. Jacobs, Ph.D.
Albert Einstein College of Medicine of Yeshiva University
Molecular genetic analysis of *Plasmodium falciparum*
Paid $25,000

Daniel E. Goldberg, M.D., Ph.D.
Washington University School of Medicine
Walter H. Lewis, Ph.D.
Washington University
Optimizing the search for new antimalarial therapeutics
Paid $50,000

Daniel L. Hartl, Ph.D.
Harvard University
Dyann F. Wirth, Ph.D.
Harvard School of Public Health
Why are there so few synonymous single nucleotide polymorphisms in *Plasmodium falciparum*
Paid $50,000

Timothy A. J. Haystead, Ph.D.
Duke University Medical Center
Mining the malarial purine-binding proteome for novel drugs and their targets
Paid $50,000

Keith A. Joiner, M.D.
Yale University School of Medicine
Mechanism of hemoglobin uptake in malaria
Paid $100,000

Kami Kim, M.D.
Vern L. Schramm, Ph.D.
Albert Einstein College of Medicine of Yeshiva University
Genetic dissection of purine salvage pathways in *Plasmodium*
Paid $25,000

Michael A. Marletta, Ph.D.
University of California-Berkeley
Heme detoxification in *Plasmodium*
Paid $50,000

Stewart H. Shuman, M.D., Ph.D.
Sloan-Kettering Institute
Targeting of mRNA cap formation for treatment of malaria
Paid $25,000

Subtotal { **Paid: $675,000**

New Investigator Awards in Molecular Parasitology

Vernon B. Carruthers, Ph.D.
Defining the proteome of toxoplasma secretory proteins
Johns Hopkins University Bloomberg School of Public Health
Paid $70,000

Daniel J. Eichinger, Ph.D.
Control of encystation-specific gene expression in *Entamoeba*
New York University School of Medicine
Paid $35,000

Theresa Gaasterland, Ph.D.
Comparative genome annotation of *Plasmodium falciparum, Leishmania major,* and *Trypanosoma brucei*
Rockefeller University
Paid $35,000

Barbara Papadopoulou, Ph.D.
Functional genomics of stage-specific gene expression in the kinetoplastid protozoan *Leishmania donovani*
Laval University Faculty of Medicine
Paid $70,000

Christian Tschudi, Ph.D.
Function of cis-splicing in trypanosome RNA
Yale University School of Medicine
Paid $35,000

Gary E. Ward, Ph.D.
Chemical genetic approach to the study of host cell invasion by *Toxoplasma gondii*
University of Vermont College of Medicine
Paid $70,000

Subtotal { **Paid: $315,000**

New Investigator Awards in Molecular Pathogenic Mycology

J. Andrew Alspaugh, M.D.
Signal transduction and pathogenicity of *Cryptococcus neoformans*
Duke University Medical Center
Paid $70,000

Tamara L. Doering, M.D., Ph.D.
Mechanisms of capsule biosynthesis in *Cryptococcus neoformans*
Washington University School of Medicine
Paid $35,000

Ashraf S. Ibrahim, Ph.D.
Molecular genetics approach for studying the role of iron permease in the virulence of *Rhizopus oryzae*
University of California-Los Angeles School of Medicine
Paid $70,000

Patrick J. Keeling, Ph.D.
Early infection and adaptation to intracellular parasitism in *Microsporidia*
University of British Columbia
Paid $35,000

Jose L. Lopez-Ribot, Pharm.D., Ph.D.
Gene and protein expression profiling in *Candida albicans* biofilms
University of Texas-San Antonio Health Science Center
Paid $35,000

Neal F. Lue, M.D., Ph.D.
Functional analysis of telomerase components in *Candida albicans*
Weill Medical College of Cornell University
Paid $35,000

Jon Woods, M.D., Ph.D.
Antisense regulation of a protein kinase gene in *Histoplasma capsulatum*
University of Wisconsin Medical School
Paid $35,000

Subtotal { **Paid: $315,000**

Scholar Awards in Molecular Parasitology

Alan A. Aderem, Ph.D.
Macrophage responses to *Leishmania* infection
University of Washington-Institute for Systems Biology
Paid $85,000

Norma W. Andrews, Ph.D.
Role of lysosome exocytosis in the cell invasion mechanism of *Trypanosoma cruzi*
Yale University School of Medicine
Paid $60,000

Paul J. Brindley, Ph.D.
Schistosome transgenesis
Tulane University School of Public Health and Tropical Medicine
Paid $85,000

Patricia J. Johnson, Ph.D.
Investigation of potential chemotherapeutic targets and the pathogenesis of the human-infective parasite *Trichomonas vaginalis*
University of California-Los Angeles School of Medicine
Paid $60,000

Marc Ouellette, Ph.D.
Functional genomics of drug resistance in *Leishmania*
Laval University Faculty of Medicine
Paid $85,000

Edward J. Pearce, Ph.D.
Role of the TGF-ß superfamily in host signaling to schistosomes
University of Pennsylvania School of Veterinary Medicine
Paid $85,000

Margaret A. Phillips, Ph.D.
Design of inhibitors for *Trypanosoma brucei* ornithine decarboxylase using a combination of structure-based approaches and combinatorial chemistry
University of Texas Southwestern Medical Center-Dallas
Paid $85,000

David S. Roos, Ph.D.
Exploring the function of the apicomplexan plastid
University of Pennsylvania
Paid $80,000

L. David Sibley, Ph.D.
Molecular pathogenesis in toxoplasmosis
Washington University School of Medicine
Paid $85,000

Samuel L. Stanley, M.D.
Pathways for amebic induction of inflammation and programmed cell death
Washington University School of Medicine
Paid $85,000

Subtotal Paid: **$795,000**

Scholar Awards in Molecular Pathogenic Mycology

Martin Bard, Ph.D.
Characterization of new target sites for antifungal intervention in the *Candida albicans* ergosterol pathway
Indiana University-Purdue University at Indianapolis
Paid $85,000

Joseph Heitman, M.D., Ph.D.
Signal transduction pathways regulating virulence of *Cryptococcus neoformans*
Duke University Medical Center
Paid $60,000

Alexander D. Johnson, Ph.D.
Analysis of a mating-type-like locus in *Candida albicans*
University of California-San Francisco School of Medicine
Paid $40,000

Elizabeth J. Keath, Ph.D.
Novel molecular and DNA vaccine approaches to *Histoplasma capsulatum*
Saint Louis University
Paid $60,000

James W. Kronstad, Ph.D.
Temperature-regulated and infection-regulated gene expression in *Cryptococcus neoformans*
University of British Columbia
Paid $85,000

Stuart M. Levitz, M.D.
Use of molecular biology to identify *Cryptococcus neoformans* antigens that stimulate cell-mediated immunity
Boston University School of Medicine
Paid $60,000

Carol S. Newlon, Ph.D.
Analysis of chromosome structure and function in the pathogenic basidiomycete *Cryptococcus neoformans*
University of Medicine and Dentistry of New Jersey
Paid $42,500

Peter A. B. Orlean, Ph.D.
Glycolipid anchoring of protein and wall biogenesis in fungal pathogens
University of Illinois at Urbana-Champaign
Paid $60,000

Michael P. Snyder, Ph.D.
Analysis of morphogenic differentiation in *Candida albicans*
Yale University
Paid $85,000

Paula Sundstrom, Ph.D.
Global regulatory circuits and candidiasis
Ohio State University College of Medicine and Public Health
Paid $85,000

Subtotal { **Paid: $662,500**

Other Grants

In addition to making competitive awards, BWF makes non-competitive grants for activities that are closely related to our major focus areas. These grants are intended to enhance the general environment for research in the targeted areas.

American Society of Tropical Medicine and Hygiene
Support for a BWF-ASTMH Fellowship in Tropical Infectious Diseases
Paid $52,000

American Society of Tropical Medicine and Hygiene
Support for the ASTMH 51st annual meeting held November 10-14, 2002, in Denver, Colorado. Specifically for support of the BWF symposium on completion of the *Plasmodium falciparum* genome
Approved $25,000 Paid $25,000

American Type Culture Collection
Support for the roll-fold poster that accompanied the *Nature* malaria genome issue
Approved $8,000 Paid $8,000

Foundation for the National Institutes of Health
Support for the purchase and distribution of the second publication of a supplement to the *American Journal of Tropical Medicine and Hygiene* titled "The intolerable burden of malaria: what's new, what's needed"
Approved $1,000 Paid $1,000

National Academy of Sciences/Institute of Medicine
Support and continued membership of the Institute of Medicine's Forum on Emerging Infections
Approved $25,000 Paid $25,000

Johns Hopkins University
Bloomberg School of Public Health
Support for the Wellcome Trust/BWF Infectious Diseases Initiative 2000
Paid $166,346

Marine Biological Laboratory
Support for Investigator in Pathogenesis of Infectious Disease awardee Dr. Heidi Goodrich-Blair to give a seminar at Woods Hole
Approved $1,000 Paid $1,000

Marine Biological Laboratory
Support for the Molecular Mycology: Current Approaches to Fungal Pathogenesis course
Paid $170,000

Marine Biological Laboratory
Support for the Biology of Parasitism: Modern Approaches course for 2003-2006
Approved $400,000 Paid $100,000

Marine Biological Laboratory
Support for the Biology of Parasitism course
Paid $75,000

Monash University
Support for an integrated *Plasmodium* genome database (PlasmoDB)
Paid $73,236

Society of Toxicology
Support for BWF New Investigator/SOT session on "DNA Damage, Repair and Related Topics" held at the 42nd Annual SOT Meeting, Salt Lake City, Utah, March 9-13, 2003
Approved $10,000 Paid $10,000

Stanford Genome Technology Center
Support for travel for malaria genome functions
Approved $1,000 Paid $1,000

Stanford University
Support for the American Society of Tropical Medicine and Hygiene symposium in Denver, Colorado, November 10-14, 2002, titled "Using genomics to understand the host-pathogen interaction."
Approved $7,500 Paid $7,500

University of Pennsylvania
Support for an integrated *Plasmodium* genome database (PlasmoDB)
Paid $269,997

Yale University
Support for the Wellcome Trust/BWF Infectious Diseases Initiative 2000
Paid $175,553

Subtotals { **Approved: $478,500** / **Paid: $1,160,632**

Totals
- Approved: $3,632,000
- Paid: $2,731,589
- Transferred/Cancelled: $64,000

Career Awards at the Scientific Interface

Lindsay G. Cowell, Ph.D.
Duke University Medical Center
Novel statistical approach to deducing the function of regulatory DNA: examples from analyses of recombination signal sequences
Approved $140,000 Paid $80,000
($360,000 approved for future faculty appointment)

Michael B. Elowitz, Ph.D.
Rockefeller University
In vivo modeling: a synthetic approach to regulatory networks
Paid $64,000

Adrienne L. Fairhall, Ph.D.
Princeton University
Neural computation, adaptation, and information processing
Approved $140,000 Paid $80,000
($360,000 approved for faculty appointment)

Jeffrey R. Kuhn, Ph.D.
Yale University
Total internal reflection fluorescence microscopy of actin branching dynamics *in vivo*
Approved $140,000 Paid $80,000
($360,000 approved for future faculty appointment)

Lisa J. Lapidus, Ph.D.
Stanford University
Dynamics of polypeptides from measurement of intramolecular contact formation
Paid $40,000

Patrick W. Nelson, Ph.D.
University of Michigan-Ann Arbor
Theoretical study of HIV-1 pathogenesis: from primary infection, through latency, to effective drug therapy or progression to AIDS
Approved $64,000 Paid $130,000
($64,000 of the original award to the University of Michigan-Ann Arbor was transferred/cancelled)

Todd E. Peterson, Ph.D.
University of Arizona College of Medicine
Ultrahigh-resolution *in vivo* imaging
Paid $64,000

Jianghong Rao, Ph.D.
University of California-Los Angeles
Imaging gene expression and protein phosphorylation in living organisms
Paid $107,600

Ronald S. Rock Jr., Ph.D.
Stanford University School of Medicine
Exploring the protein folding energy landscape at the single molecule level
Paid $64,000

Jason K. Sello, Ph.D.
Harvard Medical School
Taking a chemical genetic scalpel to a *Streptomyces* colony
Approved $140,000 Paid $80,000
($360,000 approved for future faculty appointment)

Brent R. Stockwell, Ph.D.
Massachusetts Institute of Technology
Chemical profiling of cellular disease states
Paid $64,000

Keith R. Weninger, Ph.D.
Stanford University
Single molecule study of the role of SNARE protein assisted membrane fusion in calcium-triggered neurotransmitter release
Paid $64,000

Ryohei Yasuda, Ph.D.
Cold Spring Harbor Laboratory
Visualization of biochemical signaling in single dendritic spines
Approved $140,000 Paid $80,000
($360,000 approved for future faculty appointment)

Matthew A. Young, Ph.D.
University of California-Berkeley
Allosteric regulation in cell signaling proteins
Approved $140,000 Paid $80,000
($360,000 approved for future faculty appointment)

Muhammad N. Yousaf, Ph.D.
Harvard Medical School
A surface chemistry and materials approach to develop model substrates to study PI(4,5)P2 lipid raft dependent actin polymerization
Approved $140,000 Paid $80,000
($360,000 approved for future faculty appointment)

Subtotals { **Approved: $3,564,000** / **Paid: $1,157,600** / **Transferred/Cancelled: $64,000**

Functional Genomics Innovation Awards

Listed by names, institutions, and research subjects. These special one-time awards were made in conjunction with the dedication of BWF's building in 2000. BWF also provides support for functional genomics through our other programs.

Christopher B. Burge, Ph.D.
Phillip A. Sharp, Ph.D.
Massachusetts Institute of Technology
Whole genome approaches to pre-mRNA splicing specificity and regulation
Paid $100,000

Wah Chiu, Ph.D.
Baylor College of Medicine
Gregor Eichele, Ph.D.
Max Planck Institute of Experimental Endocrinology
Spatial and temporal database of gene expression patterns of mouse brain
Paid $63,500

R. Mark Henkelman, Ph.D.
Hospital for Sick Children, Toronto
Eugene Fiume, Ph.D.
University of Toronto
Automated image analysis of genetically modified mice
Paid $100,000

Terence T. L. Hwa, Ph.D.
University of California-San Diego
Gene expression profiles based on statistical significance of clustering analysis
Paid $39,750

Sudhir Kumar, Ph.D.
Arizona State University
Computational genomic analysis to identify and dissect functionally important mutations in protein sequences
Paid $50,000

Elaine A. Ostrander, Ph.D.
University of Washington
Leonid Kruglyak, Ph.D.
Fred Hutchinson Cancer Research Center
Mapping cancer susceptibility genes in dogs by linkage disequilibrium
Paid $25,000

Gene E. Robinson, Ph.D.
University of Illinois at Urbana-Champaign
Sociogenomics: functional genomic analyses of social behavior with microarrays
Paid $100,000

Eric D. Siggia, Ph.D.
Frederick R. Cross, Ph.D.
Rockefeller University
Computational and experimental analysis of promoters in the genome of budding yeast
Paid $50,000

Oliver Smithies, D.Phil.
Nobuyuki Takahashi, M.D., Ph.D.
University of North Carolina-Chapel Hill School of Medicine
Computer simulation and animal modeling of complex genetic systems
Paid $100,000

Alan R. Templeton, Ph.D.
Washington University
Cladistic analyses of epistasis among candidate genes influencing common disease
Paid $50,000

Subtotal { **Paid: $678,251**

Institutional Awards at the Scientific Interface

Listed by name of the training program, the institution, or consortium conducting the program, and the researchers directing the program.

Cross-Disciplinary Training Program in Biophysical Dynamics
University of Chicago
Stephen J. Kron, M.D., Ph.D.
Norbert F. Scherer, Ph.D.
Paid $125,000

Graduate Program in Quantitative Biology
University of California-San Francisco School of Pharmacy
David A. Agard, Ph.D.
University of California-San Francisco School of Medicine
Ken A. Dill, Ph.D.
University of California-San Francisco School of Pharmacy
Paid $125,000

Interdisciplinary Training Program in Brain Science
Brown University
John P. Donoghue, Ph.D.
David Mumford, Ph.D.
Paid $115,238

Program in Computational Biology
Johns Hopkins University School of Medicine
Michael Paulaitis, Ph.D.
Johns Hopkins University
George D. Rose, Ph.D.
Johns Hopkins University School of Medicine
Paid $125,000

Program in Mathematical and Computational Neuroscience
Boston University
Howard B. Eichenbaum, Ph.D.
Nancy J. Kopell, Ph.D.
Paid $87,500

Program in Mathematics and Molecular Biology
Consortium of 17 laboratories and 12 institutions nationwide; administered by Florida State University
Wilma K. Olson, Ph.D.
Rutgers, the State University of New Jersey-New Brunswick
DeWitt L. Sumners, Ph.D.
Florida State University
Paid $125,000

Training Program in Biological Dynamics
Princeton University
John J. Hopfield, Ph.D.
Simon A. Levin, Ph.D.
Paid $125,000

Subtotal { **Paid: $827,738**

Other Grants

In addition to making competitive awards, BWF makes non-competitive grants for activities that are closely related to our major focus areas. These grants are intended to enhance the general environment for research in the targeted areas.

Biophysical Society
Support for the postdoctoral career development session at the 2003 annual meeting for the Biophysical Society
Approved $3,000 Paid $3,000

Canadian Genetic Diseases Network
Support for the 2003/2004 Canadian Bioinformatics Workshop series
Approved $5,000 Paid $5,000

Council of Graduate Schools
Support for a workshop on the future of graduate education, held March 19-20, 2003, in Arlington, Virginia
Approved $5,000 Paid $5,000

Institute for Theoretical Physics
(paid Regents of the University of California)
Support for interdisciplinary program titled "Biological Networks," held January 6-March 28, 2003
Approved $50,000 Paid $50,000

University of Notre Dame
Support for a series of workshops titled "Biocomplexity V: Multiscale Modeling in Biology," held August 14-17, 2003, at the University of Notre Dame
Approved $5,000 Paid $5,000

Subtotals { **Approved: $68,000**
Paid: $68,000

Totals { Approved: $1,257,911
Paid: $981,803

Student Science Enrichment Program

American Chemical Society, North Carolina Local Section
Summer Educational Experience for the Disadvantaged
Paid $59,900

Campbell University School of Pharmacy
Harnett Central Middle School Science and Technology Enrichment Program
Paid $27,700

Catawba Science Center
Science Technology Enrichment Program
Paid $40,840

Duke University
Techtronics: Hands-on Exploration of Technology in Everyday Life
Paid $60,000

Duke University Nicholas School of the Environment and Earth Sciences
Connecting Coastal Communities
Paid $28,553

Friends of Great Smoky Mountains National Park
Smoky Mountain Heights: Science Education in Western North Carolina
Approved $165,100 Paid $55,400

Lenoir-Rhyne College
Carolina Institute for the Multicultural Approach to Science
Paid $59,999

North Carolina Science Olympiad
Science Olympiad Student Enrichment Program
Approved $180,000 Paid $60,000

North Carolina State University
Performing Inquiry-Based Exploration: An Example in Using Agricultural Waste and Wastepaper to Produce New Products
Paid $22,200

Onslow Community Ministries
Sturgeon City Student Science Series
Approved $177,173 Paid $59,058

Ranger Elementary/Middle School
Wild Rides!
Approved $77,458 Paid $29,473

Shodor Education Foundation
Mentor Center at Shodor
Approved $180,000 Paid $60,000

University of North Carolina-Chapel Hill School of Medicine
Scientific Enrichment Opportunities for High School Students
Paid $59,910

Wake Forest University School of Medicine
Mini-Fellowships in Science Fields: Linking Career Choices to Student Experiences
Approved $119,680 Paid $59,840

Subtotals { **Approved: $899,411**
Paid: $682,873

Other Grants

In addition to making competitive awards, BWF makes non-competitive grants for activities that are closely related to our major focus areas. These grants are intended to enhance the general environment for research in the targeted areas.

Durham Public Education Network
Support for the K-8 Science initiative for the fourth grade magnetism and electricity unit
Approved $5,000 Paid $5,000

Grantmakers for Education
Support for general activities
Approved $3,000 Paid $3,000

Holy Cross Catholic Church
Support in lieu of honorarium for SSEP Advisory Committee Member Dr. Marian Johnson-Thompson
Approved $3,000 Paid $3,000

Morehead Planetarium and Science Center
Support for the distribution of the movie "DNA: the Secret of Life" to North Carolina schools
Approved $40,000 Paid $40,000

National Association of Academies of Science
Support for high school students to interact with scientists at the American Association for the Advancement of Science annual meeting
Approved $1,000 Paid $1,000

North Carolina Association for Biomedical Research
Support for general activities
Approved $5,000 Paid $5,000

North Carolina Center for International Understanding
Support for teachers to participate in the Learning from Korea program in November 2002
Approved $8,000 Paid $8,000

North Carolina Center for International Understanding
Support for North Carolina education leaders to participate in the Denmark Studies Program in October 2003
Approved $9,000 Paid $9,000

North Carolina Community College System
Support for North Carolina Community College leaders to visit the United Kingdom as part of a United Kingdom-North Carolina exchange program
Approved $1,500 Paid $1,500

North Carolina Science, Mathematics, and Technology Education Center
Support for general activities
Approved $2,000 Paid $2,000

North Carolina Society of Hispanic Professionals
Support for society's annual education summit
Approved $1,000 Paid $1,000

North Carolina State University
Support for a series of conferences of representatives from university science departments to discuss K-12 outreach
Approved $50,000 Paid $90,430

Pitt County Educational Foundation
Support for the Health Sciences Academy
Approved $15,000 Paid $15,000

Public School Forum of North Carolina
Support for the Institute for Educational Policymakers
Approved $180,000 Paid $75,000

Scholarship Foundation of Saint Louis
Support for general activities, directed by BWF Board Member Dr. David Kipnis
Approved $20,000 Paid $20,000

Shodor Education Foundation
Support for the Student Science Enrichment Program website
Approved $15,000 Paid $15,000

University of North Carolina-Chapel Hill
Support for convening a group of experts to help develop the Center for Functional Nanostructures
Paid $5,000

Subtotals Approved: **$358,500**
Paid: **$298,930**

Science and Philanthropy
Ad Hoc Grants

Totals { Approved: $280,050
Paid: $180,050

Communications/Science Writing

American Association for the Advancement of Science
Support for the 2003 AAAS Mass Media Science and Engineering Fellowship Program
Approved $16,000 Paid $16,000

Council for the Advancement of Science Writing
Support for the 2003 New Horizons in Science Briefing and the New Horizons Traveling Fellowship Program
Approved $20,000 Paid $20,000

Subtotals { **Approved: $36,000**
Paid: $36,000

General Philanthropy

Association of Academic Health Centers
Support for the annual meeting titled "Succeeding in Tough Times: Climbing the Ladder or Hanging On"
Approved $5,000 Paid $5,000

Association of American Medical Colleges
Support for a nationwide survey of interdisciplinary research centers and institutes in medical schools
Approved $10,000 Paid $10,000

Council on Foundations
Support for general activities
Approved $39,600 Paid $39,600

Foundation Center
Support for general activities
Approved $7,500 Paid $7,500

Southeastern Council of Foundations
Support for general activities
Approved $5,000 Paid $5,000

University of North Carolina-Chapel Hill
Support for seminar by New Investigator Beverly Wendland
Approved $450 Paid $450

Subtotals { **Approved: $67,550**
Paid: $67,550

Science Policy

American Association for the Advancement of Science
Support for the AAAS Center for Science, Technology, and Congress
Approved $150,000 Paid $50,000

Research!America
Support for the 435 Project, which advocates for increased funding for medical research
Approved $25,000 Paid $25,000

Subtotals { **Approved: $175,000**
Paid: $75,000

Special Award

Nantucket Conservation Foundation
Grant in lieu of honorarium for Investment Committee Member Curt Livingston
Approved $1,500 Paid $1,500

Subtotals { **Approved: $1,500**
Paid: $1,500

Totals
- Approved: $5,136,612
- Paid: $6,976,612
- Transferred/Cancelled: $975,000

Clinical Scientist Awards in Translational Research

During the fiscal year, some award recipients change institutions or modify the terms of their award at their current institution, or both. In these cases, BWF's policy is to cancel the remaining portion of the original award and, as necessary, approve a new award. When the award recipient has changed institutions, the new award is made to the new institution; when the award recipient has not moved but has modified the terms, the new award is made to the current institution. In the following descriptions, the name of the award recipient is listed first, the title of the project is listed second, the award recipient's current institution is listed third, and the amount approved or paid to the institution is listed fourth. For award recipients who either changed institutions or modified their awards, the portion of the award paid to the original institution, as well as any portion that was transferred or cancelled, is listed last, in parentheses.

Sunil K. Ahuja, M.D.
HIV-1 AIDS pathogenesis: bridging the gap between host genotype and HIV transmission/disease phenotype
University of Texas-San Antonio Health Science Center
Paid $150,000

David M. Altshuler, M.D., Ph.D.
Genomic approaches to the genetics of type 2 diabetes and response to antidiabetic medication
Massachusetts General Hospital
Paid $150,000

Nina Bhardwaj, M.D., Ph.D.
Vaccination of HIV-1 positive individuals by antigen-pulsed dendritic cells
New York University School of Medicine
Approved $300,000 Paid $75,000
($75,000 of the original award to Rockefeller University was paid; $300,000 of the original award to Rockefeller University was transferred/cancelled)

Cameron S. Carter, M.D.
Multimodal brain imaging and the pharmacotherapy of cognitive disability in schizophrenia
University of Pittsburgh School of Medicine
Paid $150,000

Judy H. Cho, M.D.
Characterization of expression patterns in monocyte-derived cells in inflammatory bowel disease
University of Chicago Pritzker School of Medicine
Paid $150,000

Gilbert Chu, M.D., Ph.D.
Cancer treatment by genome-wide transcription scanning
Stanford University Medical Center
Paid $75,000

George Q. Daley, M.D., Ph.D.
Chemotherapy and stem cell transplantation in leukemia
Harvard Medical School
Approved $750,000

Robert B. Darnell, M.D., Ph.D.
Detection and activation of tumor-specific killer cells in animal models and cancer patients
Rockefeller University
Paid $150,000

Claire M. Doerschuk, M.D.
Response of neutrophils during inflammatory lung disease
Case Western Reserve University School of Medicine
Paid $150,000

Robert W. Doms, M.D., Ph.D.
Chemokine receptors as new targets for HIV-1 therapeutics
University of Pennsylvania School of Medicine
Paid $75,000

Jeffrey A. Drebin, M.D., Ph.D.
Targeted suppression of B-catenin in colorectal cancer
Washington University School of Medicine
Paid $150,000

Brian J. Druker, M.D.
Mechanism-based therapy for chronic myelogenous leukemia
Oregon Health and Science University
Paid $150,000

Barry A. Finette, M.D., Ph.D.
Mechanisms of malignant transformation in humans
University of Vermont College of Medicine
Paid $150,000

Glenn I. Fishman, M.D.
Gap junction channels as novel anti-arrhythmic targets
New York University School of Medicine
Paid $150,000

Thomas F. Gajewski, M.D., Ph.D.
Development of a second-generation melanoma vaccine
University of Chicago Pritzker School of Medicine
Paid $150,000

Lisa M. Guay-Woodford, M.D.
Genetic modifiers in recessive polycystic kidney disease: implications for pathogenesis and therapeutics
University of Alabama-Birmingham School of Medicine
Paid $150,000

Eva Guinan, M.D.
Extending the donor pool by inducing alloantigen specific T-cell anergy *ex vivo* for human hematopoietic stem cell transplantation
Dana-Farber Cancer Institute
Paid $150,000

Barbara L. Hempstead, M.D., Ph.D.
Growth factor regulation of coronary angiogenesis
Weill Medical College of Cornell University
Paid $150,000

Marshall S. Horwitz, M.D., Ph.D.
Therapeutic inhibition of aberrant protease activity in inherited neutropenias
University of Washington School of Medicine
Paid $150,000

Thomas J. Hudson, M.D.
Genomic approaches to identify genes predisposing to asthma
McGill University Faculty of Medicine
Paid $150,000

Daniel C. Javitt, M.D., Ph.D.
NMDA-based treatment development for schizophrenia
New York University School of Medicine
Paid $150,000

Jane E. Koehler, M.D.
Genomic and clinical correlates of human *Bartonella quintana* infection
University of California-San Francisco School of Medicine
Approved $750,000

Jonathan D. Licht, M.D.
Targetting aberrant repression as a therapeutic strategy in hematological malignancy
Mount Sinai School of Medicine
Paid $150,000

Alex E. MacKenzie, M.D., Ph.D.
Cytoprotective NAIP and XIAP genes: identification of activation pathways and inducing agents
University of Ottawa Faculty of Medicine
Paid $75,000

David M. Markovitz, M.D.
New approaches to inhibiting HIV replication
University of Michigan-Ann Arbor
Approved $750,000

Joseph M. McCune, M.D., Ph.D.
Regulation of human thymic function *in vivo*
University of California-San Francisco School of Medicine
Paid $150,000

M. Juliana McElrath, M.D., Ph.D.
Induction of cellular immunity in HIV-1 exposed seronegative individuals
Fred Hutchinson Cancer Research Center
Paid $150,000

Elizabeth M. McNally, M.D., Ph.D.
Microvascular spasm in the progression of cardiomyopathy
University of Chicago
Paid $150,000

Sofia D. Merajver, M.D., Ph.D.
Genetic determinants of aggressive breast cancer phenotypes: translation to the clinic
University of Michigan-Ann Arbor
Approved $750,000

Hector D. Molina, M.D.
Mechanisms of complement-induced abnormalities in fetomaternal tolerance
Washington University School of Medicine
Paid $150,000

Jason D. Morrow, M.D.
Isoprostanes as markers and mediators of oxidant stress in humans
Vanderbilt University Medical Center
Paid $150,000

Anthony J. Muslin, M.D.
Signaling mechanisms in cardiovascular disease
Washington University School of Medicine
Paid $150,000

W. Cam Patterson, M.D.
Oxidative profiles in cardiovascular diseases
University of North Carolina-Chapel Hill School of Medicine
Approved $750,000

Mark R. Philips, M.D.
Endomembrane trafficking of Ras: novel molecular targets for anticancer agents
New York University School of Medicine
Paid $150,000

Steven A. Porcelli, M.D.
Defining the protective human CD8+ T cell response against *Mycobacterium tuberculosis*
Albert Einstein College of Medicine of Yeshiva University
Paid $150,000

Daniel J. Rader, M.D.
Novel therapeutic approach to atherosclerosis through modulation of HDL metabolism
University of Pennsylvania School of Medicine
Paid $150,000

W. Edward Robinson Jr., M.D., Ph.D.
Structure-function analyses of clinically relevant HIV integrases
University of California-Irvine College of Medicine
Paid $150,000

Don C. Rockey, M.D.
Cellular and molecular basis of portal hypertension: an endothelialopathy in cirrhosis
Duke University Medical Center
Paid $150,000

Howard A. Rockman, M.D.
Novel molecular therapeutic strategies in heart failure: role of beta-adrenergic receptor desensitization
Duke University Medical Center
Paid $75,000

Antony Rosen, M.B., Ch.B.
Altered structure and clearance of autoantigens during apoptosis: implications for autoimmunity
Johns Hopkins University School of Medicine
Paid $150,000

Marc E. Rothenberg, M.D., Ph.D.
Experimental analysis of eosinophil-associated gastrointestinal inflammation
University of Cincinnati College of Medicine
Paid $150,000

David T. Scadden, M.D.
Developing control mechanism-based stem cell therapies
Massachusetts General Hospital
Paid $150,000

Christian W. Schindler, M.D., Ph.D.
Intervention of IL-5 signaling: a therapeutic paradigm for asthma
Columbia University College of Physicians and Surgeons
Paid $75,000

Ann Marie Schmidt, M.D.
Novel therapeutic strategy for the prevention and treatment of diabetic complications: antagonism of receptor for advanced glycation end products (RAGE)
Columbia University College of Physicians and Surgeons
Paid $75,000

Mark H. Siegelman, M.D., Ph.D.
Functionally activated lymphocyte CD44 in the initiation and perpetuation of autoimmune disease
($375,000 of the original award to the University of Texas Southwestern Medical Center-Dallas was transferred/cancelled)

Joyce M. Slingerland, M.D., Ph.D.
Resistance to tamoxifen: a consequence of altered $p27^{Kip1}$ regulation during breast cancer progression
University of Miami School of Medicine
Approved $120,264 Paid $120,264
($75,000 of the original award to the University of Toronto Faculty of Medicine was transferred/cancelled)

Donald Small, M.D., Ph.D.
Translating FLT3 inhibition into improved therapy for pediatric AML and infant ALL
Johns Hopkins University School of Medicine
Approved $750,000

Dennis J. Templeton, M.D., Ph.D.
Stress signaling inhibitors potentiate genotoxin-induced apoptosis in a human colon tumor model
University of Virginia Medical Center
Approved $131,349 Paid $131,349

Matthew L. Warman, M.D.
Delineating the proteins and pathways that maintain human joints and their potential for treating heritable and acquired forms of arthritis
Case Western Reserve University School of Medicine
Paid $150,000

Mark J. Yeager, M.D., Ph.D.
Structure and function of cardiac gap junction membrane channels
Scripps Research Institute
Paid $75,000

Hagop Youssoufian, M.D.
($225,000 of the original award to Baylor College of Medicine was transferred/cancelled)

Subtotals
Approved: **$5,051,612**
Paid: **$5,876,612**
Transferred/Cancelled: **$975,000**

New Investigator Awards in the Basic Pharmacological Sciences

Peter J. Belshaw, Ph.D.
Combinatorial synthesis of non-ribosomal peptide-based electrophilic libraries
University of Wisconsin-Madison
Paid $70,000

Anton M. Bennett, Ph.D.
p21 Ras signaling by protein tyrosine dephosphorylation
Yale University School of Medicine
Paid $70,000

Pehr A. B. Harbury, Ph.D.
DNA display: *in vitro* evolution of small molecules
Stanford University School of Medicine
Paid $35,000

Neil L. Kelleher, Ph.D.
Genome-proteome correlations in respiratory pathogens: an experimental approach for identification of new pharmacological targets
University of Illinois at Urbana-Champaign
Paid $35,000

Calvin J. Kuo, M.D., Ph.D.
Physiologic and pathologic roles of vascular endothelial growth factor
Stanford University School of Medicine
Paid $70,000

Carla Mattos, Ph.D.
Surface features of the Ral GTPase obtained from the multiple solvent crystal structures and from its complex with RalBP1 and calmodulin
North Carolina State University
Paid $35,000

David P. Siderovski, Ph.D.
GoLoco motif-derived peptides as selective G-protein "perturbagens"
University of North Carolina-Chapel Hill School of Medicine
Paid $70,000

Scott K. Silverman, Ph.D.
Phototriggered folding approaches to RNA structural motifs and RNA-protein interactions
University of Illinois at Urbana-Champaign
Paid $70,000

Erik J. Sontheimer, Ph.D.
Reversible control of RNA structure with small biarsenical ligands
Northwestern University
Paid $35,000

Joseph Tsien, Ph.D.
Novel pharmacogenetic approach to neuronal signaling
Princeton University
Paid $35,000

Hongtao Yu, Ph.D.
Molecular investigation of transitions and checkpoints in mitosis
University of Texas Southwestern Medical Center-Dallas
Paid $35,000

Subtotal { **Paid: $560,000**

New Investigator Awards in the Toxicological Sciences

Raffi V. Aroian, Ph.D.
Bacillus thuringiensis toxicity and resistance in nematodes
University of California-San Diego
Paid $35,000

Virginia W. Cornish, Ph.D.
In vivo screening for enzymatic activity
Columbia University
Paid $35,000

Mohanish P. Deshmukh, Ph.D.
Caspase activation during apoptosis: a novel mechanism of regulation in neurons
University of North Carolina-Chapel Hill School of Medicine
Paid $70,000

Bevin P. Engelward, Sc.D.
Fluorescent detection of loss heterozygosity in mammals
Massachusetts Institute of Technology
Paid $35,000

James M. Ford, M.D.
Transcriptional regulation of damage-inducible DNA repair genes
Stanford University School of Medicine
Paid $35,000

Su Guo, Ph.D.
Mechanism of action of neurotoxins that induce parkinsonism: a molecular genetic study in zebrafish
University of California-San Francisco School of Pharmacy
Paid $70,000

Carla M. Koehler, Ph.D.
Mitochondrial biogenesis in health and disease: assembly of the mitochondrial inner membrane
University of California-Los Angeles
Paid $35,000

Anna K. Mapp, Ph.D.
Small molecules for reprogramming gene expression
University of Michigan College of Pharmacy
Paid $70,000

Terry L. Sheppard, Ph.D.
Chemical toxicology of oxidative DNA damage lesions
Northwestern University
Paid $70,000

Subtotal { **Paid: $455,000**

Other Grants

In addition to making competitive awards, BWF makes non-competitive grants for activities that are closely related to our major focus areas. These grants are intended to enhance the general environment for research in the targeted areas.

National Academy of Sciences
Support for the Institute of Medicine's Clinical Research Roundtable
Approved $40,000 Paid $40,000

University of Vermont and State Agricultural College
Support for the Clinical Research Alliance meeting, held March 14-16, 2003, in Baltimore, Maryland
Approved $45,000 Paid $45,000

Subtotals { **Approved: $85,000**
Paid: $85,000

Information for Applicants

The Burroughs Wellcome Fund makes approximately 90 percent of our grants through competitive award programs, which support investigators in targeted areas of basic scientific research that have relevance to human health.

Most of BWF's award programs are open only to citizens or permanent residents of the United States and Canada. (Programs with different requirements are noted in the descriptions that follow.) Awards are made with the advice of our advisory committees, which comprise scientists and educators selected for their expertise in the program areas. Program application deadlines for the 2005 award series are listed in the "Program Application Deadlines" section on page 71.

Most grants are made only to degree-granting institutions on behalf of individual researchers, who must be nominated by their institution. Institutions receiving grants must be tax-exempt 501(c)(3) organizations. Government agencies, such as the National Institutes of Health and the Centers for Disease Control and Prevention, generally are not eligible for grants.

Throughout the following program descriptions, references to M.D. and Ph.D. degrees include all types of medical and scientific doctoral degrees.

BWF believes that diversity within the scientific community enhances the well-being of the research enterprise; therefore, we encourage applications from women and from members of underrepresented minority groups.

BWF does not support activities that are primarily clinical in nature (such as disease diagnosis and treatment) or primarily related to health care and health care policy. We generally do not provide support for research projects or other activities outside our competitive programs, nor do we generally support endowments, development campaigns, ordinary operating expenses, capital facilities and equipment, or publications.

To obtain the most up-to-date information about our award programs, visit our website at www.bwfund.org

Burroughs Wellcome Fund

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Basic Biomedical Sciences

Career Awards in the Biomedical Sciences
These awards are made in honor of Gertrude B. Elion, D.Sc., and George H. Hitchings, Ph.D., who shared the 1988 Nobel Prize in Physiology or Medicine and were long associated with the Burroughs Wellcome Fund. The awards are intended to foster the development and productivity of biomedical researchers who are early in their careers and to help them make the critical transition to becoming independent investigators. The grants provide $500,000 over five years to bridge advanced postdoctoral training and the first three years of faculty service. Recipients may spend part of the grant period at institutions in the United Kingdom. BWF expects to award up to 20 of these grants annually. Approximately half of the awards will go to researchers with a Ph.D. degree and half to those with an M.D. or M.D.-Ph.D. degree. Candidates must have completed at least 12 months but not more than 48 months of postdoctoral research training by the application deadline. For candidates with M.D. degrees, postdoctoral training excludes clinically oriented residencies that do not contain a major research component. Researchers who hold a faculty appointment as an assistant professor or the equivalent, or who know they will hold such an appointment within a year of the application deadline, are not eligible.

Infectious Diseases

Investigators in Pathogenesis of Infectious Disease
These awards provide new opportunities for accomplished investigators at the assistant professor level to study pathogenesis, with a focus on the intersection of human and pathogen biology. The program is intended to shed light on the overarching issues of how human hosts handle infectious challenge. These five-year grants, which provide $80,000 per year, are intended to give recipients the freedom and flexibility to pursue new avenues of inquiry and higher-risk research projects that hold potential for advancing significantly the biochemical, pharmacological, immunological, and molecular biological understanding of how infectious agents and the human body interact. BWF is particularly interested in work focused on the host, as well as host-pathogen studies originating in viral, bacterial, fungal, or parasite systems. Studies in these areas may have their root in the pathogen, but the focus of the work should be on the effects on the host at the cellular and/or systemic levels. Excellent animal models of human disease are within the scope of the program. Candidates must have an established record of independent research and hold a tenure-track position as an assistant professor or equivalent at a degree-granting institution in the United States or Canada. Up to eight of these grants will be awarded annually.

Interfaces in Science

Career Awards at the Scientific Interface
These awards are intended to foster the early career development of researchers with backgrounds in the physical/computational sciences whose work addresses biological questions and who are dedicated to pursuing a career in academic research. Candidates are expected to draw from their training in a scientific field other than biology to propose innovative approaches to answer important questions in the biological sciences. The grants provide up to $500,000 over five years to support up to two years of advanced postdoctoral training and the first three years of a faculty appointment. BWF expects to award up to eight of these grants in 2004. Candidates must have a Ph.D. degree in physics, chemistry (physical, theoretical, or computational), mathematics, computer science, statistics, or engineering. Exceptions will be made only if the candidate can demonstrate significant expertise in one of these areas, evidenced by publications or advanced course work. This program is open to U.S. and Canadian citizens and permanent residents as well as temporary residents whose H1B visa was granted on or after January 1, 2002. Degree-granting institutions many nominate up to two candidates.

Translational Research

Clinical Scientist Awards in Translational Research
These awards are intended to foster the development and productivity of established independent physician-scientists who will strengthen translational research, the two-way transfer between work at the laboratory bench and clinical medicine. The grants provide $750,000 over five years ($150,000 per year). BWF expects to award up to eight of these grants annually. We are interested particularly in supporting investigators who will bring novel ideas and new approaches to translational research and who will mentor the next generation of physician-scientists. Proposed activities may draw on the many recent advances in the basic biomedical sciences—including such fields as biochemistry, cell biology, genetics, immunology, molecular biology, and pharmacology—that provide a wealth of opportunities for studying and alleviating human disease. Candidates generally must be affiliated with a medical school; candidates at other types of degree-granting institutions (including schools of veterinary medicine, public health, and pharmacy) will be considered only if they can demonstrate a plan for coordinating with institutions that provide the patient connection essential for translational research. Candidates must have an M.D. or M.D.-Ph.D. degree and hold an appointment or joint appointment in a subspecialty of clinical medicine. In exceptional circumstances, non-M.D. candidates will be considered if their work is likely to contribute significantly to the clinical enterprise; these candidates should hold an appointment or joint appointment in a clinical department. Candidates must be tenure-track investigators at the late assistant professor level or the associate professor level, or hold an equivalent tenure-track position, at the time of application. Candidates must present evidence of already having established an independent research career, as this is not a "new investigator" award. Individuals holding the rank of professor are ineligible.

Science Education

Student Science Enrichment Program
These awards are limited to nonprofit organizations in BWF's home state of North Carolina. BWF provides around $1 million annually for this program, and grants provide up to $60,000 per year for three years. The program's goals include improving students' competence in science, nurturing their enthusiasm for science, and interesting them in pursuing careers in research or other science-related areas. The awards are intended to support projects that provide creative science enrichment activities for students in the sixth through twelfth grades who have shown exceptional skills and interest in science, as well as those who may not have had an opportunity to demonstrate conventional "giftedness" in science but are perceived to have high potential. The projects must enable students to participate in hands-on scientific activities and pursue inquiry-based avenues of exploration—an educational approach that has proven to be an effective way to increase students' understanding and appreciation of the scientific process. Project activities must take place outside of the usual school environment, such as after school, on weekends, or during vacation periods. Projects may be conducted all year, during the school year, or during the summer. Eligible organizations include colleges and universities, community groups, museums and zoos, public and private schools, scientific groups, and others that can provide experiential activities for middle school and high school students. We encourage partnerships—for example, between scientific groups and school systems or between universities and community groups. Industries may participate in collaboration with nonprofit organizations that assume the lead role.

Science and Philanthropy

BWF makes noncompetitive grants for activities that fall outside of our competitive award programs but are closely related to our targeted areas, such as career development of scientists or the pathogenesis of infectious disease. We place special priority on working with nonprofit organizations, including government agencies, to leverage financial support for our targeted areas of research, and on encouraging other foundations to support biomedical research. Proposals should be submitted to BWF in the form of a letter, which should be no more than five pages. Applicants should describe the focus of the activity, the expected outcomes, and the qualifications of the organization or individuals involved; provide certification of the sponsor's Internal Revenue Service tax-exempt status; and give the total budget for the activity, including any financial support obtained or promised. Proposals are given careful preliminary review, and those deemed appropriate are presented for consideration by BWF's Board of Directors.

Program Application Deadlines

2005 Award Series

Basic Biomedical Sciences

Career Awards in the Biomedical Sciences	October 1, 2004

Infectious Diseases

Investigators in Pathogenesis of Infectious Disease	November 1, 2004

Interfaces in Science

Career Awards at the Scientific Interface	May 3, 2004
Institutional Awards at the Scientific Interface	To be determined

Science Education

Student Science Enrichment Program	April 12, 2004

Translational Research

Clinical Scientist Awards in Translational Research	September 1, 2004

Science and Philanthropy

Received all year

Advisory Committees

The Burroughs Wellcome Fund uses advisory committees for each competitive award program to review grant applications and make recommendations to BWF's Board of Directors, which makes the final decisions. We select members of these committees for their scientific and educational expertise in the program areas. In addition, BWF uses a financial advisory committee to help in developing and reviewing the Fund's investment policies. This committee is appointed by and reports to the Board of Directors.

Career Awards in the Biomedical Sciences

Jack Antel, M.D.
McGill University Faculty of Medicine

William Chin, M.D.
Eli Lilly and Company

Patricia K. Donahoe, M.D. (Cochair)
Massachusetts General Hospital
Harvard Medical School

Elaine Fuchs, Ph.D.
Howard Hughes Medical Institute
Rockefeller University

Margaret K. Hostetter, M.D.
Yale University School of Medicine

Thomas M. Jessell, Ph.D.
Columbia University

Lawrence C. Katz, Ph.D.
Howard Hughes Medical Institute
Duke University Medical Center

Stanley J. Korsmeyer, M.D.
Howard Hughes Medical Institute
Dana-Farber Cancer Institute
Harvard Medical School

George M. Langford, Ph.D.
Dartmouth College

Martin M. Matzuk, M.D., Ph.D.
Baylor College of Medicine

Roderick R. McInnes, M.D., Ph.D.
University of Toronto
Hospital for Sick Children

J. Anthony Movshon, Ph.D.
New York University

Suzanne R. Pfeffer, Ph.D.
Stanford University School of Medicine

John F. Sheridan, Ph.D.
Ohio State University

Ian A. Wilson, D.Phil., D.Sc., F.R.S. (Cochair)
Scripps Research Institute

Christopher Wylie, Ph.D.
University of Cincinnati College of Medicine

Investigators in Pathogenesis of Infectious Disease

Arturo Casadevall, M.D., Ph.D.
Albert Einstein College of Medicine

Mary K. Estes, Ph.D.
Baylor College of Medicine

Diane E. Griffin, M.D., Ph.D.
Johns Hopkins University Bloomberg School of Public Health

Philippe Gros, Ph.D.
McGill University Faculty of Medicine

Stephen L. Hajduk, Ph.D.
University of Alabama Marine Biological Laboratory

Philippa Marrack, Ph.D.
Howard Hughes Medical Institute
National Jewish Medical and Research Center

David G. Russell, Ph.D.
Cornell University College of Veterinary Medicine

Magdalene So, Ph.D.
Oregon Health and Sciences University

P. Frederick Sparling, M.D. (Chair)
University of North Carolina-Chapel Hill School of Medicine

Interfaces in Science

Laurence F. Abbott, Ph.D.
Brandeis University

Robert H. Austin, Ph.D.
Princeton University

Carlos Bustamante, Ph.D.
Howard Hughes Medical Institute
University of California-Berkeley

Susan N. Coppersmith, Ph.D.
University of Wisconsin-Madison

Douglas A. Lauffenburger, Ph.D. (Cochair)
Massachusetts Institute of Technology

Michael C. Reed, Ph.D.
Duke University

Susan S. Taylor, Ph.D. (Cochair)
Howard Hughes Medical Institute
University of California-San Diego School of Medicine

Clinical Scientist Awards in Translational Research

Martin J. Blaser, M.D.
New York University Medical Center

John W. Griffin, M.D. (Cochair)
Johns Hopkins University School of Medicine

Alan Krensky, M.D.
Stanford University Medical Center

Beverly S. Mitchell, M.D.
University of North Carolina School of Medicine

John E. Niederhuber, M.D.
University of Wisconsin Medical School

Jennifer M. Puck, M.D. (Cochair)
National Human Genome Research Institute
National Institutes of Health

Marlene Rabinovitch, M.D.
University of Toronto Faculty of Medicine
University of Toronto Hospital for Sick Children

Christine E. Seidman, M.D.
Howard Hughes Medical Institute
Harvard Medical School

Michael J. Welsh, M.D.
Howard Hughes Medical Institute
University of Iowa College of Medicine

Wayne M. Yokoyama, M.D.
Howard Hughes Medical Institute
Washington University School of Medicine

New Investigator Awards in the Pharmacological or Toxicological Sciences

This program was discontinued after the 2001 award series; however, the advisory committees will continue to monitor awardees' progress.

Pharmacological Sciences Subcommittee

Lorraine J. Gudas, Ph.D.
Weill Medical College of Cornell University

T. Kendall Harden, Ph.D.
University of North Carolina-Chapel Hill School of Medicine

Lee E. Limbird, Ph.D. (Chair)
Vanderbilt University Medical Center

Victor Ling, Ph.D.
British Columbia Cancer Research Centre

Palmer Taylor, Ph.D.
University of California-San Diego School of Medicine

Jeffrey M. Trent, Ph.D.
Translational Genomics Research Institute

Toxicological Sciences Subcommittee

Barbara F. Hales, Ph.D.
McGill University Faculty of Medicine

Philip Hanawalt, Ph.D.
Stanford University

Victor A. Levin, M.D.
University of Texas M. D. Anderson Cancer Center

Baldomero M. Olivera, Ph.D.
University of Utah

Stephen H. Safe, D.Phil.
Texas A&M University College of Veterinary Medicine

Thomas J. Slaga, Ph.D. (Chair)
AMC Cancer Research Center

Student Science Enrichment Program

Julia Clark, Ph.D.
National Science Foundation

Luciano Corazza, Ph.D.
University of California-Berkeley

G. Thomas Houlihan, Ph.D.
Council of Chief State School Officers

Marian Johnson-Thompson, Ph.D.
National Institute of Environmental Health Sciences

Carolyn Mahoney, Ph.D.
Elizabeth City State University

Willie Pearson Jr., Ph.D.
Georgia Institute of Technology

Sylvia Sanders, Ph.D.
Educator, Palo Alto, California

Sally G. Shuler (Chair)
Smithsonian Institution

Liz Woolard
W. G. Enloe High School

Douglas Y. Yongue
North Carolina General Assembly

Investment Committee

The committee is composed of four members from outside BWF and three members from BWF's Board of Directors. The board's chair, BWF's president, and BWF's vice president for finance also serve on the committee as nonvoting members.

Stephen D. Corman (Chair)
BWF Board of Directors

Michael Even
Citigroup

Geoff Gerber
Twin Capital Management

W. Curtis Livingston
Western Asset Management

I. George Miller, M.D.
BWF Board of Directors

Walter Niemasik
Snyder Capital Management

Philip R. Tracy
BWF Board of Directors

Board of Directors

Enriqueta C. Bond, Ph.D.

President
Burroughs Wellcome Fund

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Professor of Physics and Molecular
and Cell Biology
University of California-Berkeley

Gail H. Cassell, Ph.D.

Vice President, Infectious Diseases
Drug Discovery Research
and Clinical Investigation
Eli Lilly and Company
Lilly Research Laboratories

Stephen D. Corman

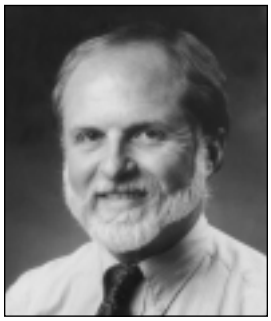
Founder and former Chair
and Chief Executive Officer
PharmaLink Inc.

Marye Anne Fox, Ph.D.

Chancellor
North Carolina State University

Phil Gold, M.D., Ph.D.

Douglas G. Cameron Professor of Medicine
McGill University
Professor of Physiology and Oncology
Montreal General Hospital



Albert James Hudspeth, M.D., Ph.D.

Investigator,
Howard Hughes Medical Institute
F. M. Kirby Professor and Head,
Laboratory of Sensory Neuroscience
Rockefeller University

I. George Miller, M.D.

John F. Enders Professor of Pediatric Infectious Diseases
Professor of Epidemiology and Molecular Biophysics and Biochemistry
Yale University School of Medicine

Mary-Lou Pardue, Ph.D.

Boris Magasanik Professor of Biology
Massachusetts Institute of Technology

James F. Strauss II, M.D., Ph.D.

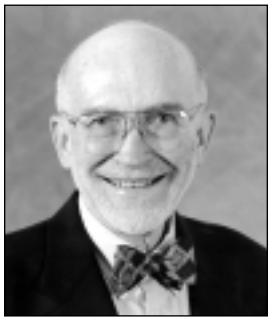
Luigi Mastroianni Jr. Professor of Obstetrics and Gynecology
University of Pennsylvania Medical Center
Director, Center for Research on Reproduction and Women's Health
Hospital of the University of Pennsylvania

Judith Swain, M.D.

Arthur L. Bloomfield Professor of Medicine
Chair, Department of Medicine
Stanford University Medical Center

Philip R. Tracy

Of Counsel
Smith, Anderson, Blount, Dorsett, Mitchell & Jernigan, L.L.P.



Jean D. Wilson, M.D.

Charles Cameron Sprague Distinguished Professor of Biomedical Science
University of Texas Southwestern Medical Center-Dallas

Executive

LEFT TO RIGHT:
Enriqueta C. Bond, Ph.D., President
Scott G. Schoedler, Vice President, Finance

Administration, Finance, Meetings, and Technology

SITTING, LEFT TO RIGHT:
Glenda H. Oxendine, Document/Web Specialist
Kenneth P. Browndorf, Senior Asset and Accounting Manager
Martie H. Gregory, Senior Manager, Facility and Administrative Services
Judy McConnell, Librarian/Secretary
Sam Caraballo, Systems and Web Engineer

STANDING, LEFT TO RIGHT:
Jennifer Caraballo, Accountant
Wendell E. Jones, Technology Coordinator
Brent Epps, Administrative Support
Betsy Stewart, Secretary/Receptionist
Catherine L. Voron, Meeting Professional
Barbara J. Evans, Administrative Meeting Assistant

Programs and Communications

SITTING, LEFT TO RIGHT:
Debra A. Vought, Senior Program Associate
Rolly L. Simpson Jr., Senior Program Associate
Jean A. Kramarik, Senior Program Associate
D. Carr Thompson, Senior Program and Communications Officer

STANDING, LEFT TO RIGHT:
Debra J. Holmes, Administrative Program Assistant
Mirinda J. Kossoff, Communications Officer
Melanie B. Scott, Senior Program Associate and Database Specialist
Nancy S. Sung, Ph.D., Senior Program Officer
Victoria P. McGovern, Ph.D., Senior Program Officer
Martin Ionescu-Pioggia, Ph.D., Senior Program Officer

Contact Information for Major Programs

Staff e-mail addresses and focus areas

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Interfaces in Science; Translational Research
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To obtain information about programs

Burroughs Wellcome Fund
The most up-to-date information about our programs, including complete application information, can be found on our website at www.bwfund.org

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