



By Marjorie Roberts

This hasn't been the best of years for the U.S. Army abroad and it doesn't look all that bright for the near future. But at home the Army has, among other jobs, the rewarding task of giving money away to deserving medical scientists. About the same time American troops were fighting in the first Gulf War, Congress initiated a medical research funding program in specific diseases. Using skills developed in managing battlefield medical innovations, the Army began investing in collaborations that would lead to advances in medical research. Since its inception in 1992, the Department of Defense Congressionally Directed Medical Research Programs (CDMRP) has awarded New York Medical College 11 grants totaling more than \$5 million. This year, named awardees will receive more than \$210,000 as the Army carries out its mission "to find and fund the best research to eradicate diseases and support the warfighter for the benefit of the American public."

The program originated from a special partnership among the public, Congress and the Department of Defense, beginning with a strong nudge from grassroots advocacy. The first appropriation was made for breast cancer research. In 2006 Congress appropriated \$350 million for the United States Army Medical Research and Materiel Command to pass along to the CDMRP. The research directorate is currently managing grants for prostate and ovarian research in addition to breast cancer. It has also assembled an unusual mix of ailments on which to focus—neurofibromatosis, military health, tuberous sclerosis complex, chronic myelogenous leukemia and prion diseases, as well as other specified areas. (Tuberous sclerosis complex is similar to neurofibromatosis, but symptoms are concentrated in the central nervous system. Prion diseases include bovine spongiform encephalopathy, or "mad-cow disease.")

## Fruit flies and marrow

To the delight of research administrators and applicants, the Army funds its grants up front, rather than over a spec-

ified period. Two members of the College faculty are past recipients: Marietta Y. Lee, Ph.D., and Joseph Wu, Ph.D., professors of biochemistry and molecular biology. Following are the faculty scientists who are currently receiving Army funds for use in their laboratories:

- **Frances Hannan, Ph.D.**, assistant professor of cell biology and anatomy, Neurofibromatosis Research Program, New Investigator Award to study signal transduction; "Functional Analysis of Human NF1 by Expression in *Drosophila melanogaster*" – \$681,435. Dr. Hannan also received a Concept Award, "A Transgenic Model for Learning Defects: Role of NF1 in *Drosophila* Visuo-Spatial Learning" – \$105,860.
- **Koko Murakami, Ph.D.**, research assistant professor of cell biology and anatomy, Neurofibromatosis Research Program, named awardee for a Concept Award for "Characterization of NF1 protein ubiquitination" – \$105,860.

As for deciding on what gets funded, the Army has come up with a novel addition to the decision making process. Besides the typical peer review by scientists who contribute their time by meeting as a group to score an application, people with the disease in question sit right at the table and score the applications along with the scientists.

- **Richard J. Zeman, Ph.D.**, associate professor of cell biology and anatomy, Peer-Reviewed Medical Research Program for "Control of Spinal Cord Injury by Stereotactic X-irradiation" – \$1,573,916.
- **Raj K. Tiwari, Ph.D.**, associate professor of microbiology and immunology, Breast Cancer Research Program, Concept Award for "Estrogen Mobilizes Circulating Bone Marrow Progenitor Cells to Promote Tumor Neovasculation: Lessons from Ischemic Model Provide a Novel Breast Cancer Target" – \$118,500.
- **Jen-Wei Chiao, Ph.D.**, professor of medicine, of immunology and of urology, Prostate Cancer Research Program, Idea Development Award for

"Chemoprevention of Prostate Cancer by Phenethyl Isothiocyanate" – \$557,633.

Anything an applicant ever needed to know about Army funding is available for the asking on the CDMRP website at <http://cdmrp.army.mil>. From the Army's standpoint, the exposure it provides, plus the availability of electronic filing, have been a godsend, says Gail Whitehead, public affairs coordinator of CDMRP. She is a civilian employed by one of the contracting agencies that provide staff for the program in Fort Detrick, Md.

## Bye hard copy

"Before electronic filing, we would have a line of UPS trucks waiting to deliver truckloads of paper applications by the deadline. But after 9/11, we had to become a secure Army post," she says, putting into perspective what a little computer disk can do for filing an application. As for deciding on what gets

funded, the Army has come up with a novel addition to the decision making process. Besides the typical peer review by scientists who contribute their time by meeting as a group to score an application, people with the disease in question sit right at the table and score the applications along with the scientists. "The consumer review presents the layman's perspective—what is good or bad from a patient's point of view," says Ms. Whitehead. Compassion is a potent element of the process when survivors are consulted. As for the investigators, how fortunate they are to have their scientific interests coincide with those in Congress who hold the purse strings and the Army managers who cut them loose.



In the laboratory of Frances Hannan, Ph.D., assistant professor of cell biology and anatomy, you'll find plenty of gags about flies, like the flyswatter in the shape of Australia, her native continent. But Dr. Hannan is seriously devoted to her fruit flies—transgenic drosophila—which she trains and tests in her efforts to unravel the mysteries of neurofibromatosis Type 1.

**Frances Hannan, Ph.D.**, relies on a very tiny model—the fruit fly—to study a not-so-rare, devastating disease, neurofibromatosis Type 1 (NF1), inflicting benign and malignant tumors on patients who suffer learning difficulties and attention deficits as well. She has been cultivating fruit flies, into which human genes are inserted, for this purpose her entire career. “Transgenic *Drosophila* have only four chromosomes, there are lots of mutations available and they have short life spans. The fly genome was one of the first to be sequenced,” Dr. Hannan says. Inherited neurofibromatosis affects 1 in 3,500 people in the U.S., not all with obvious symptoms.

After other investigators showed that lovastatin, a cholesterol lowering drug, can rescue mutant mice with learning deficits by working through the Ras signaling pathway, Dr. Hannan found that her flies also use the Ras protein for long term memory, and further depend on the cAMP pathway for short term memory. Just how you discover this in fruit flies, she reveals, is through train-

ing—by exposing them to a certain odor that is associated with an electric shock. Flies carrying mutations in the NF1 gene not only have difficulty learning, but also have a defective long term memory. Roughly 100 flies are used during a learning test, but when an experiment involves visual learning, it's one fly at a time. “We use a flight simulator, the inside of a rotating drum, to teach a fruit fly to fly toward a visual cue, and it is punished [with infrared heat] if it heads in the wrong direction...The fly uses a different part of the brain for visual cues, and we can disrupt gene function in specific areas because we know what regions are involved...We

study this because children with NF1 have particular difficulty in judgment of line orientation,” Dr. Hannan says.

**Koko Murakami, Ph.D.**, also drawn to study NF1, collaborates with Dr. Hannan on the devastating and complex disorder that may be on the brink of yielding to drug therapy. She proposes to examine how the function of the NF1 protein (neurofibromin) is controlled by the addition of ubiquitin groups. Ubiquitins are small proteins that tag larger proteins for degradation. Just where they attach, and how, is the focus of this study of ubiquitin machinery. Blocking neurofibromin ubiquitination would result in elevated levels of the neurofibromin protein, and may improve tumor suppressor activity, cognitive function and other symptoms caused by defects in signaling pathways that result from reduced levels of neurofibromin. The long term goal is to find a drug that will stop or accelerate the process.





The U.S. Army has been supporting the research of Richard J. Zeman, Ph.D., left, associate professor of cell biology and anatomy, as he searches for clues to alleviate the ordeal of spinal cord injury. The condition afflicts upwards of 12,000 new victims each year, a large proportion of them members of the armed forces. Dr. Zeman's research associates, Nengtai Ouyang, Ph.D., center, and Xialing Wen, M.S., round out the investigative team.

Richard J. Zeman, Ph.D., wants to learn how to stop spinal cord injury, especially the contusion kind that bruises the spine, common after auto accidents, football mishaps and war. Veterans represent a large proportion of the 12,000 new cases each year, and a prevalence of 240,000 chronic cases in the U.S. The cord responds to injury with “a profound loss of neural tissue and functional capacity,” leaving young soldiers with irreversible paralysis that can last for decades. An important goal of rehabilitation is to increase neuromuscular strength and function and reduce healthcare dependence.

Dr. Zeman started by using clenbuterol/albuterol to oppose muscle atrophy in injured rats. Clenbuterol

stops the inflammatory process that destroys tissue and goes on to promote locomotive recovery. But the drug has side effects and may not readily pene-



trate injured tissue. Only methylprednisolone, a steroid, has been shown to work in humans, yet only modestly. Treatment must begin right after injury and suppressing the immune system opens the door to infections later on.

In conjunction with the Department of Radiation Medicine, and based on pre-clinical successes, Dr. Zeman is investigating the role of glutathione as a neuroprotective agent. He and Chitti R. Moorthy, M.D, professor of clinical radiation medicine and acting chairman of the Department of Radiology, are using x-irradiation (which always penetrates) delivered stereotactically to decrease the paralysis that follows an injury. “We know that radiation activates glutathione, an antioxidant present in our tissues, which is consumed after injury and must be replenished. We can regain locomotive ability by blocking the oxidative stress that causes injury,” says Dr. Zeman. “The bottom line is we want to find the best antioxidant mechanism of action.”



Raj K. Tiwari, Ph.D., foreground, becomes animated whenever he talks about his studies of metastatic breast cancer. His equally ardent team members are, from left: graduate student Devyani Chaudhuri, research assistant professor Ashok Badithe, Ph.D., and post-doctoral fellow Robert Suriano, Ph.D.

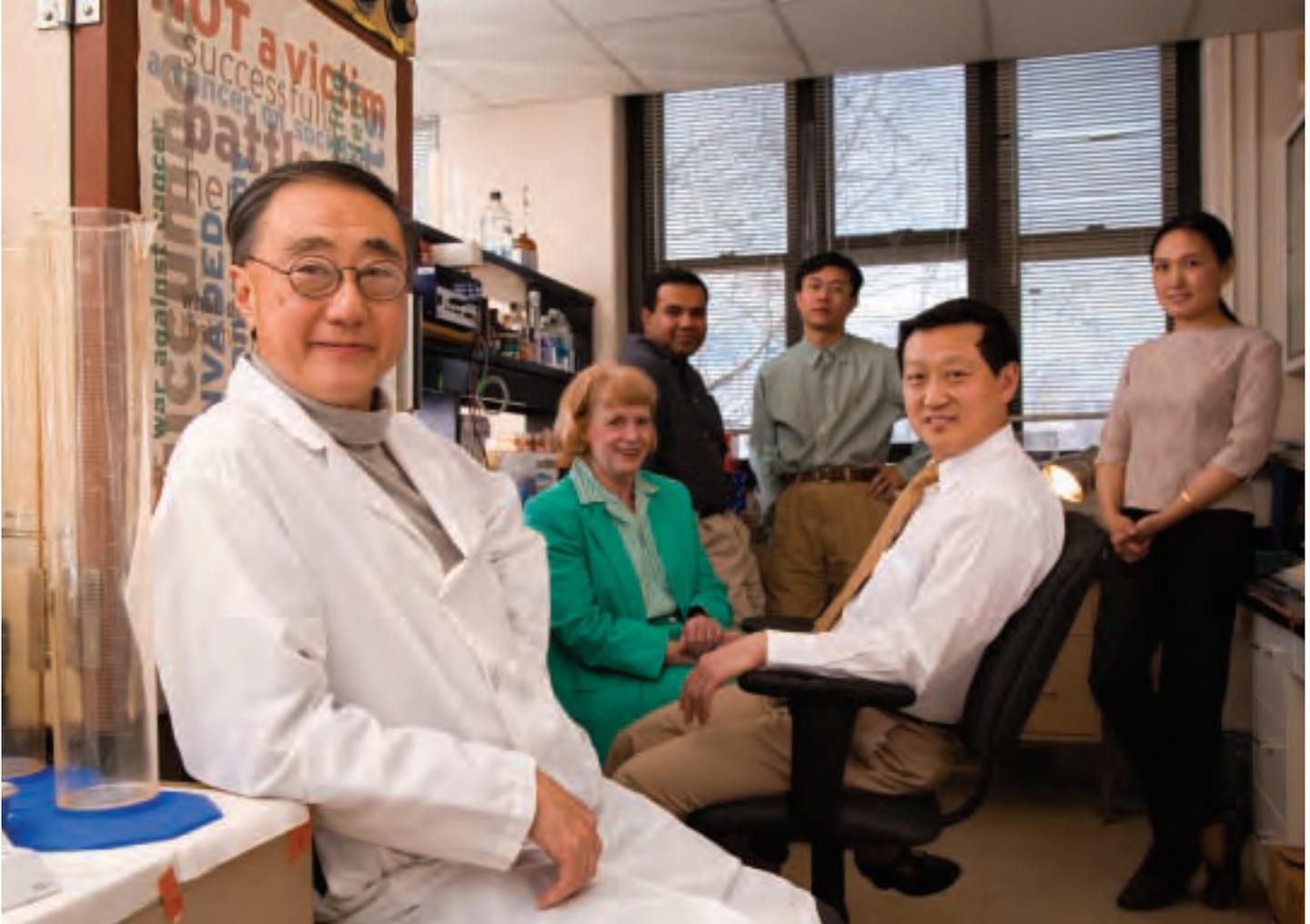


Raj K. Tiwari, Ph.D., received his first Army grant at the College for nearly \$500,000 for taking on the challenges of immunotherapy of prostate cancer in the absence of defined tumor

specific antigens. This new award for breast cancer research singles out estrogen as the gang leader of metastases—the mobilizer of circulating bone marrow-derived endothelial progenitor cells looking to get into the bloodstream and find a new place to set up shop. As in most solid tumors, neo-vascularization or blood vessel formation is essential to the process. “But it is a double-edged sword,” says Dr. Tiwari. “You need vessels to funnel drugs to kill the tumors, but these same vessels form an escape route for

cells to enter the bloodstream, initiating the process of metastasis.

“First we have to identify which cells are leaving the bone marrow and entering the tumor in our mouse model. We think it is cd31... Despite the fact that 60 percent of all breast cancers are estrogen dependent and most breast cancers start out as estrogen responsive, no mechanistic study has yet examined how estrogen mobilizes circulating bone marrow-derived endothelial progenitor cells, which home to implanted breast carcinoma and promote tumor growth and spread.”



J.W. Chiao, Ph.D., foreground, professor of medicine, is finding ways to use the isothiocyanates in cruciferous vegetables as a way to restore certain damaged genes back to an inactive state. Fellow members of Dr. Chiao's team are (from left): Ruth Gallagher, B.S., M.B.A., administrator; Nasir Ahmed, M.D., clinical research coordinator; Sean Lin, M.D., Ph.D., and Jean Feng, M.D., M.S., fellows; and DeLong Liu, M.D., Ph.D., associate professor of medicine.

**Jen-Wei Chiao, Ph.D.**, can really explain to former President George Bush why he should eat broccoli. It was his laboratory that produced the original report that isothiocyanates, present naturally in cruciferous vegetables, may be one of the most responsible dietary factors for preventing prostate cancer. Cruciferous is the classification for the cabbage and mustard family that also includes turnips, radish, cauliflower, watercress, Brussels sprouts and, of course, broccoli.

Prostate cancer is the most commonly diagnosed cancer among men in the U.S. Growth and maintenance of the prostate is influenced by the hormone androgen, and any abnormality of the androgen receptor is a decisive factor in the failure of treatment in advanced cases. "If we can lower the supply of androgen we can inhibit the cancer," Dr. Chiao says. "We have demonstrated that a family of

isothiocyanates from different species of cruciferous vegetables induces growth arrest and cell death in human prostate cancer cells in culture and in mouse cancer models." Repressing the androgen receptor—at the transcriptional level by inhibiting transcription factor Sp1 and at the post translational level by accelerating protein degradation,—are the important mechanisms of action.

Dr. Chiao's lab has demonstrated that isothiocyanates can inhibit the aberrant epigenetic effects (excess DNA methylation) in the DNA and protein complex, which regulate the way genes make proteins. This is how a key detoxifying protein, GSTP1, present in normal prostate tissues but missing in more than 90 percent of prostate tumors, is recovered. In Dr. Chiao's experiments, he reactivated the GSTP1 gene and

restored the detoxifying function in the cancer cells. "We have also used isothiocyanates to reactivate other silenced genes in cancer cells, making them regain their normal functions. It is this self regulation that can overcome the cancer



changes. It is also the basis of prostate cancer prevention by the vegetables," he says "... You know how broccoli smells when it is cooking? That's the isothiocyanates you smell!" 🍷