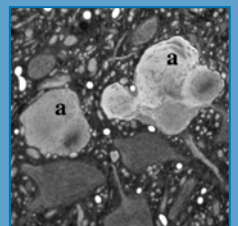


# CROET

Putting science to work for working Oregonians



CROET  
2004-2005  
ANNUAL  
REPORT



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# Mission, Purpose, and Mandate

CROET, the Center for Research on Occupational and Environmental Toxicology at OHSU, is dedicated to the promotion of health and safety in the workforce. Through basic and applied research, education, and outreach, CROET seeks to prevent disease and disability among working Oregonians and their families, during their employment years and throughout retirement.



# Message From the Director

Dear fellow Oregonians:

So many positive and interrelated developments have taken place in 2004-05 that it seems appropriate to describe CROET's progress during these years in this single report. For readers unfamiliar with CROET, the Center for Research on Occupational and Environmental Toxicology is a research institute of Oregon Health & Science University (OHSU) that seeks to address and solve health and safety problems in Oregon workplaces. By mandate of the State of Oregon, CROET was founded in 1988 and placed at OHSU to maximize the effectiveness of the institute's programs in research, education, and outreach to working Oregonians and beyond. The great breadth and diverse nature of CROET's programs are detailed at [www.ohsu.edu/croet](http://www.ohsu.edu/croet). Our sister web site at [www.CROETweb.com](http://www.CROETweb.com) provides a rich variety of occupational safety and health information.

CROET's researchers are putting science to work for working Oregonians. We aggressively leverage our dedicated base support from the Workers' Benefit Fund to maximize federal and other research dollars that can be used to advance the CROET mission. In cooperation with the OHSU School of Medicine, Oregon State University, and Battelle Pacific Northwest, CROET houses two major center grants from the National Institutes of Health. One is a Superfund Basic Research Center that addresses how to assess health threats and safely clean up hazardous waste sites, such as the Portland Harbor Superfund Site. The second brings CROET-OHSU together with other universities (Duke, University of North Carolina) and institutions (Fred Hutchinson Cancer Research Center, MIT, National Institute of Environmental Health Science) in a prestigious Toxicogenomics Research Consortium ([www.niehs.nih.gov/research/supported/centers/trc/index.cfm#structure](http://www.niehs.nih.gov/research/supported/centers/trc/index.cfm#structure)) that delves into the most intimate details of the biological response of cells to chemical exposures and common diseases. Examining and interpreting gene expression change is becoming a major tool in medicine for diagnosis, for determining chemical and drug sensitivities and effectiveness, and for personalized risk assessment and treatment based on genetic subtleties of individuals and populations. Add these two NIH center grants to the many individual research and education awards won by CROET's world-class scientists, and one can see how we leveraged \$1.00 from the State's Workers' Benefit Fund to bring an additional \$2.40 of federal and private support to Oregon.

CROET's research results in discovery, discoveries are spread through education, and education and training promote disease and injury prevention, and more effective methods to diagnose and treat illness at an early, curable stage. CROET researchers translate their research findings from bench to workplace in ways that benefit every Oregonian. Described in the following pages is CROET's Chemical Risk Information Service, which provides employers and employees with access to information on the hazards of workplace chemicals. We back this up with CROET's Toxicology Information Center that offers detailed assessments on workplace and other hazards that Oregonians face, and [www.CROETweb.com](http://www.CROETweb.com) that provides an organized directory of occupational safety and health resources. To promote healthy and safe behaviors at work, two CROET faculty have licensed novel computer-based training programs to a newly created Oregon-based start-up company. Other faculty members have created a high-tech company that seeks to commercialize novel molecular biology methods for repair of skin damaged at work, and in the prevention of cancer. Funds generated from these new companies will help support further research, contribute to the advancement of Oregon's portfolio of companies, and increase opportunities for leading-edge jobs.

The origin of CROET's success is found in the diverse disciplines and methodological approaches that work in synergy in this unique Oregon research institute. While the strengths and influence of individual faculty members are evident from their grant successes, scholarly publications, invited contributions to the editorial boards of scientific journals, and their service on local, regional, and national committees, it is the special mix of talent and ambition that is indispensable to producing tangible results for working Oregonians. Key results include: molecular, cellular, tissue, human and population studies that advance understanding of common diseases affecting the workforce; communication of new health and safety knowledge throughout the state and beyond; prevention of avoidable injuries through effective training and assessment; and detailed analyses and reporting of occupational fatalities that hopefully will help prevent workplace deaths.

Respectfully submitted,



Peter S. Spencer, PhD, FRCPATH  
CROET Director and Senior Scientist

# CROET: a Resource for Oregon

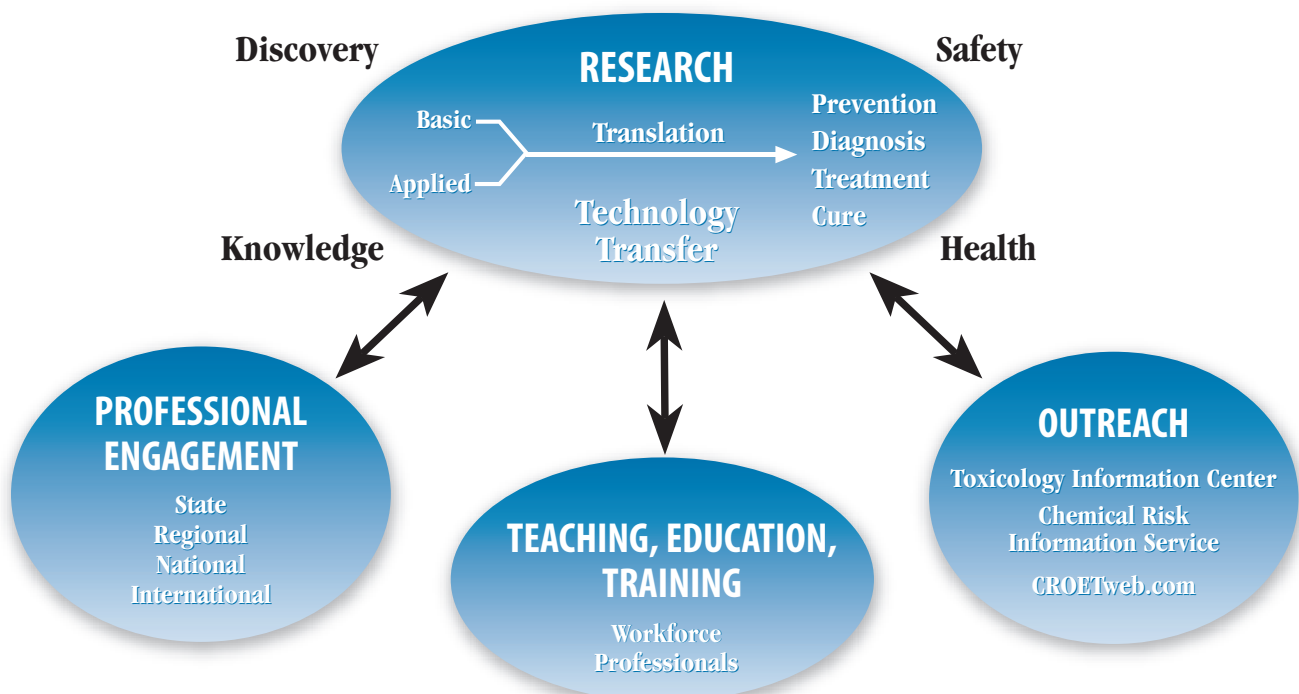
CROET conducts research on the basic biology of workplace-related injury and disease as well as research related to workplace performance and occupational exposure. CROET also participates in doctoral and postdoctoral educational programs to train the next generation of scientists, and provides updates for health and safety specialists to ensure that the latest scientific advances are translated into enhanced workplace safety. Through its outreach efforts, CROET serves as an information conduit to Oregon workers, employers, labor, and the general public.

Applied research addresses workplace hazards, often spurred by specific safety issues of immediate concern to Oregon's workers. Research is focused on surveillance of workplace and environmental problems and on prevention of injury in agriculture, service industries, and construction. This research has short-term payoffs. Examples: (1) surveillance is identifying unrecognized trends in Workers' Compensation claims, suggesting new prevention priorities; (2) computer-based training has been developed for respirator safety, pesticide exposures, and ergonomics in drywall finishing, and training effectiveness is under study; and (3) agriculture workers are monitored for exposure to pesticides and adverse nervous system health effects, and are given safety training.

Basic research is focused on nerve and muscle damage and repair, occupational/environmental exposures and their consequences, DNA damage, and cancer. This research requires prolonged commitment and synergy among investigators and has a long-term payoff. It is applicable to many diseases and disorders including those associated with the workplace and those that arise from other causes (e.g., genetic, environmental) that plague Oregonians during their working years and into retirement. While this is important for Oregonians, it obviously has a wider impact. Thus, most of the funding for CROET's research in these areas is supported by grants from the National Institutes of Health and from other federal sources. Examples of what CROET scientists are studying include: (1) how nerves grow, how they connect (form synapses) with other nerve cells and with muscles, and how to enhance their regenerative potential — all of which are critical to post-injury recovery; (2) how environmental exposures trigger DNA damage and cancer, and how mutations in specific genes disrupt cell function; and (3) how the brain and other organs function in normal conditions and following exposure to chemicals and drugs.

## State Mandate:

Conduct basic and applied research, outreach and education to address Oregon's occupational health needs.



# Committees and Scientific Leadership

## OHSU President's Advisory Committee for CROET

Donald Baird, PhD, Oregon State University  
Hon. Alan Bates, DO, Oregon State Representative  
Jim Craven, American Electronics Association  
John Kirkpatrick, Painters District Council  
Hon. Mary Gallegos, Oregon State Representative  
Hon. David Nelson, Oregon State Senator

Lou Savage, Department of Consumer & Business Services  
Marilyn Schuster, Oregon OSHA  
Hon. Frank Shields, Oregon State Senator  
Bob Shiprack, Oregon Building Trades  
Lisa Trussel, Associated Oregon Industries

## Recognition of CROET Faculty and Staff (2004–2005)

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### Membership on NIH Study Sections or NIH Council

Banker – NIH Synapses, Cytoskeleton, and Trafficking Study Section  
Spencer – NIEHS National Advisory Environmental Health Sciences Council

### Membership on Committees Outside OHSU (selected)

Anger – Gulf War and Health, Institute of Medicine  
Banker – Executive Committee, Nanobiotechnology Center, Cornell University  
Lein – U.S. EPA Science Advisory Panel for Dimethoate  
– National Science Foundation Review Panel for Developmental Neuroscience  
Rischitelli – Review for U.S. Preventive Services Task Force on Blood Lead Testing of Asymptomatic Children  
– Chair NIOSH State-based Fatality Assessment and Control Evaluation (FACE) Coordinating Committee  
– Oregon Workers' Compensation Division Medical Advisory Committee  
Spencer – Chair of Steering Committee, NIH-NIEHS Toxicogenomics Research Consortium  
– Committee on Emerging Issues and Data on Environmental Contaminants  
– Board of Environmental Studies and Toxicology, National Research Council  
– Medical Follow-Up Agency, Institute of Medicine  
– Advisory Panel for the Study of Long-term Health Effects of Participation in Project SHAD (Shipboard Hazard and Defense), Institute of Medicine

### Invited Presentations at Major Symposia or Meetings

Allen – Winter Conference on Brain Research  
– American Society of Photobiology  
– Society of Research on Biological Rhythms  
Anger – Hanninen Lecture: 9th International Symposium on Neurobehavioral Methods & Effects in Occupational & Environmental Health  
Lein – Joint NIEHS and ACC meeting: Developmental Toxicology and Fetal Basis of Adult Disease  
– Keynote at UC Davis Conference for Environmental Health Sciences  
– European Center for the Validation of Alternative Methods (ECVAM)  
Lloyd – Gordon Conference: Genetic Toxicology  
Patton – FASEB Annual Experimental Biology Meeting  
– American Society for Neurochemistry  
Shyng – NIH workshop: “The role of protein misfolding and misprocessing in disease”  
Spencer – George H. Germann Memorial Lecture, American College of Occupational and Environmental Medicine  
Turker – Indiana University Professor Milton Taylor Symposium  
– OSU/CROET Satellite Meeting of the Environmental Mutation Society: Mismatch Repair Responses to DNA Lesions

### Editorial Board of Top Tier Journals

Banker – *Journal of Neurocytology*  
Lloyd – *Journal of Biological Chemistry*  
– *Chemical Research in Toxicology*  
Rischitelli – *Environmental Health Perspectives* (Associate Editor)  
Spencer – *Environmental Health Perspectives*  
Turker – *Mutation Research*  
– *Science of Aging Knowledge & Environment* (online version of *Science*)  
Lein – *Toxicology Letters*

# CROET's Areas of Emphasis

## Education and Outreach Programs

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CROET's Education and Outreach Programs have four goals:

- Provide scientifically accurate information on Oregon's occupational issues — continuously on the Internet and daily with scientific interpretation for complex issues through the Toxicology Information Center (TIC)
- Offer educational programs on Oregon's occupational needs to medical providers and health and safety specialists
- Train health professionals who will investigate Oregon's occupational safety and health issues in the future
- Provide the scientific expertise to help Oregon industry and labor evaluate occupational health and safety questions

## Research

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### Surveillance, Applications and Outreach

- Cellular mechanisms that control sleep-wake cycles relevant to shift workers
- Computer-based and other training methods to enhance worker safety training
- Agricultural, construction, and transportation worker populations

### Injury and Recovery of the Nervous System and Muscles

- Assessing nerve cell protein dynamics using imaging
- Using nanotechnology to enhance nerve growth
- Factors that govern the accuracy of nerve synapse formation
- Pharmacological interventions to enhance (e.g., speed) nerve regeneration
- Genetic models of nerve maldevelopment

### Chronic Disease and Working Safely

- Effects of pesticide exposures assessed using exposure biomarkers and behavioral testing
- Toxicants that disrupt protein transport in neurons
- Defining and studying models of chronic disease (asthma, neurodegenerative, diabetes)

### Integrity of DNA (DNA damage, genetic alterations, and disease)

- Role of DNA repair in protecting the nervous system from effects of chemicals
- Gene silencing and cancer
- Mutations induced by ionizing irradiation, oxidative stress, and other genotoxins
- Ion channel mutations that underlie diseases

### Selected 2004-2005 Accomplishments and Awards

- OR-FACE fatality investigation project highlights logging, mobile machinery, transportation, and workers over age 65
- New CROET faculty member studying transportation highlights performance measures to reduce first-flight crashes
- Computer-based training program developed in CROET shown effective in shop floor workers (food service)
- Evidence found of very low levels of pesticides in Oregon children, increasing during the growing season
- More than 1,250 links to occupational safety and health topics, organized for ready use, are found on CROETweb.com
- Asthma associated with organophosphorous but not pyrethroid pesticides in animal studies
- Important mechanisms of neuronal transport revealed that may help explain why diseases occur or recovery fails
- Model of metabolic disease in the obese developed
- Improved understanding of organic solvent neurotoxicity leads to ability to predict which solvents can damage the nervous system
- Two OHSU/CROET spinoff companies achieve early milestones
- CROET faculty and staff recognition continues to grow: NIH study sections, national and statewide committees, invited presentations, major editorial boards, and international appointments



# 2004-2005 CROET Highlights

## Surveillance, Applications and Outreach

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CROET conducts workplace surveillance so that prevention and research needs can be identified, and applications research to bring the benefits of science to the workplace floor. It also reaches out to provide education and information to the Oregon workforce and beyond.

### Oregon Fatality Assessment and Control Evaluation (OR-FACE) Program

Dr. Gary Rischitelli leads the Oregon Fatality Assessment and Control Evaluation (OR-FACE) program that tracks, investigates, and reports on occupational fatalities in Oregon. Each incident is investigated, entered in a database, and codes are added for industry, occupation, and event. During 2004 and 2005, OR-FACE recorded 62 and 67 fatalities, respectively. OR-FACE investigates incidents in specific national and local target areas of concern, and each year produces about 12 investigation reports with safety recommendations. During 2004-05, OR-FACE also published two hazard alerts — one on electrocution from high-voltage power lines during highway work and another on the unexpected finding that parked vehicles are a common cause of fatal injury. In 2005, OR-FACE published its first annual report, summarizing data from the program's first full year of operation in 2003. The report charted frequencies by age, gender, race/ethnicity, day, time, month, county, industry, occupation, and event and included an abstract of each incident. Principal areas of concern were highlighted in relation to logging, mobile machinery, and transportation. In the 2004 annual report, an additional area of concern was observed in an elevated fatality rate among workers aged 65 and over, including a high incidence of falls and suicide. OR-FACE investigation reports and other publications are available on the program's website ([www.ohsu.edu/croet/face](http://www.ohsu.edu/croet/face)). Investigation reports from Oregon and other FACE states are also available in the electronic library maintained by the National Institute for Occupational Safety and Health ([www.cdc.gov/niosh/face](http://www.cdc.gov/niosh/face)), which funds the program.

### Computer-based Training Effective for Shop Floor Workers (food services)

In collaboration with an urban hospital in Portland, Dr. Kent Anger provided interactive computer-based safety training to workers in a food services department that supplies food to hospital patients, visitors, and staff. The food services workers evaluated the training very positively. Based on tests given before and after the training, knowledge improved significantly. Generalization of the knowledge to the workplace was confirmed by increased accuracy in answering on-the-job questions that required application of knowledge to the work setting. Observations were also made of work practices and workplace conditions before and after the training. Problematic kitchen conditions, such as puddles, decreased after-training and after-adjustment for increasing production/workload. Work practice improvement was seen in three-fourths of the workers. These findings demonstrate that the benefits of computer-based safety instruction extend to blue collar workers who do not usually receive computer-based training, which is only rarely studied. It is even more rare for research to study and report changes in reaction (did they like the training?), knowledge, and behavior or work practice change, which adds confidence to the findings. This and other studies demonstrate, in an experimentally rigorous way, that computer-based training can be used with workers on the shop floor, not just in offices where it is most typically used. This work was published in the *Journal of Safety Research*.

### Evidence of Increased Pesticide Metabolic By-Products in Agricultural Areas

Dr. William Lambert and others at CROET have been investigating the possibility that children of migrant farm workers are at increased risk of exposure to organophosphate (OP) pesticides due to “carry-home” transport processes and residential location. Although this at-risk status is generally recognized, few available reports describe the extent of this exposure among agricultural communities. It is very difficult to measure the very low levels of pesticide exposures, so Dr. Lambert and others at CROET quantified the metabolic products of organophosphate pesticides in samples of urine from 176 children, 2-6 years of age. The children were from three Oregon communities hosting differing agricultural industries: pears, cherries, and fruit berries. Up to three spot samples of urine were collected from children at the beginning, mid-point, and end of their parents' work seasons. The median levels of dimethylthiophosphate (DMTP), the most commonly detected metabolite of OP pesticides, was 2.5 to 4 times higher in urine samples from children in the agricultural communities when compared to a reference group of children who lived in an urban community and whose parents did not work in agriculture. After controlling for confounders, the median level of DMTP in children in the pear community was 1.92 times higher than the level in children of the berry community and 1.75 times higher than the level in children of the cherry community. DMTP levels increased across the work season only within the berry community. Levels decreased in the cherry community and remained constant in the pear community. This variation across time in pesticide levels within the children who were followed demonstrates the need for multiple urine samples to accurately characterize longer term and/or cumulative exposure. This variability could be attributed to the types and amounts of organophosphate pesticides used, the timing of applications and degradation of residues in the environment, work operations and hygiene practices, the proximity of housing to orchards and fields, or the movement of these working families.

## Improved Training for Beginning Flight Students

Flight students have the highest risk of landing accidents when flying solo during their first 30 hours of training. Since training innovations may help prevent these potentially fatal crashes, Dr. Ryan Olson investigated the potential benefits of one type of interactive training for new flight students. Personal Computer-Based Aviation Training Devices (PCATDs) are increasingly sophisticated and affordable, but are currently approved only for limited instrument training with experienced students. Dr. Olson hypothesized that PCATDs could be used strategically to prevent landing crashes among novice pilots. In 2005, Dr. Olson published evidence in the *Journal of Aviation/Aerospace Education and Research* that experimental PCATD training during the first 30 flight hours may improve multiple performance measures. Since no measurable harm was found, early PCATD training should be tested more aggressively as a risk-management intervention.

## CROET Outreach Expansion Continues

CROETweb.com is the Center's occupational safety and health resource directory that provides information 24 hours a day, seven days a week.

- CROETweb topics expanded from 46 different English topics in 2004 to 72 topics
- Spanish-language topic pages expanded from 37 in 2004 to 60 topic pages
- More than 1,250 links are posted on the CROETweb page
- A monthly CROETweb update newsletter is now sent electronically to almost 600 addresses. It had more than 19,000 downloads in 2004-2005.

Toxicology Information Center (TIC): Directed by Fred Berman, DVM, PhD, the Toxicology Information Center provides current information for those with questions about chemical, biological, physical and other agents encountered in the workplace and elsewhere. In 2004-2005, Dr. Berman handled more than 200 requests for such information from physicians and nurses, occupational safety and health professionals, business owners, and the general working public. Inquiries covered a range of issues. Chemical agents of concern included solvents, heavy metals, insecticides, fungicides, and herbicides. Physicians often called seeking information on a variety of potentially occupation-related health complaints. The TIC is open from 7:30 a.m. to 4 p.m., Monday through Friday. Walk-in visitors have access to a variety of resources, including computers, databases, government reports, textbooks, and journals that are devoted to toxicology-related issues.

### Symposia

- When Employees' Personal Lives Interact with Occupational Safety and Health
- The Multidimensional Causes of Accidents and Injuries

### Exhibits

- Central OR-OSHA; Southern OR-OSHA; Cascade Western Pulp & Paper (OR-OSHA)
- Northwest Occupational Health Conferences
- Governor's Occupational Safety and Health (GOSH) Conference
- NexCon Construction Summit
- Oregon Governor's Fire Service Summit
- Healthcare Ergonomics
- Oregon Worker Compensation Educational Conference

### Collaboration/Advisory

- Developed Outreach Strategic Plan (2004-2006), which was approved by the OHSU President's CROET Advisory Committee

## Injury and Recovery of the Nervous System and Muscles

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CROET scientists conduct basic research that examines the causes of injury to nerves and muscles in order to identify protective, preventive, and recovery methodologies for such injuries.

### Organophosphate but not Pyrethroid Pesticides Associated with Airway Muscle Spasm

Over the last 20 years, asthma rates have soared to epidemic levels. According to the United States Center for Disease Control, between 1980 and 1994, the number of people with asthma in the United States increased by 75 percent, and today this disease afflicts more than 15 million people in this country. Very little is known about what causes asthma or how it may be prevented. Recent studies by Dr. Pamela Lein, in collaboration with Dr. Allison Fryer, a professor in the Department of Physiology and Pharmacology at OHSU, suggest that organophosphorous pesticides (OPs) may initiate or aggravate an asthma attack. Using a well-established guinea pig model of asthma, these researchers demonstrated that OPs increase airway hyperreactivity. OPs cause the airway to constrict, which is a hallmark characteristic of asthma. Their studies further suggest that OPs cause increased airway constriction by altering the function of the nerves that control contraction of the muscles lining the airway. OP effects on airway hyperreactivity



and nerve function were observed at relatively low doses. These low doses did not inhibit the activity of cholinesterase, which is the enzyme that breaks down acetylcholine, the neurotransmitter released by nerves that cause airway smooth muscle to contract. Interestingly, cholinesterase inhibition is used by a number of state and federal regulatory agencies as a biomarker to indicate whether humans have been exposed to potentially toxic levels of OPs (this is the mechanism by which OPs kill insects). Thus, this research indicates that OPs may trigger airway hyperreactivity in animals and potentially in humans at exposure levels that are generally considered to be safe. Moreover, the most recent data from Dr. Lein's studies indicate that guinea pigs that have been sensitized to antigen, which is a type of allergic reaction, are even more sensitive to OPs and exhibit airway hyperreactivity in response to much lower doses than non-sensitized guinea pigs. Since 70 to 80 percent of asthmatic patients also have allergies, these observations suggest that environmental levels of OPs may pose a significant environmental risk factor for asthma in humans. (Fryer, Lein, et al., *American Journal of Physiology: Lung, Cellular and Molecular Physiology*, 2004; 286: L963-9)

### Important Mechanisms of Neuronal Protein Transport Revealed

Nearly every aspect of neuronal function depends on the delivery of proteins from the cell body, where they are made, to their appropriate destinations in axons or dendrites. Nerve cells are especially vulnerable to disruptions of protein transport because they have complicated shapes and because their axons are so long. Exposure to chemicals in the workplace or in the environment can disrupt protein transport, leading to neurological disease. Likewise, many of the neurodegenerative diseases of aging, such as Alzheimer's disease, are also associated with alterations in protein transport. Dr. Gary Banker's program is studying the molecular mechanisms that underlie the accuracy and efficiency of protein transport in order to define new molecular targets for therapies to ameliorate or cure diseases that are caused by defects in protein transport. His laboratory initially developed methods to visualize vesicles as they move into axons or dendrites. In 2004, this approach was used to study how proteins that should go to different destinations are directed into the correct vesicle. Dr. Banker's team found that axonal and dendritic proteins contain different localization signals, analogous to address labels, which govern how proteins are packaged into vesicles. Mistakes in these localization signals cause the proteins to be directed to the wrong place. For example, using their assay for imaging vesicles, the Banker team showed that mutations in a dendritic localization signal caused the protein to be packaged in the same carrier as axonal proteins, resulting in its transport to an incorrect destination. Mistakes in protein localization like this can disrupt the electrical and chemical signals that nerve cells use to communicate with each other and with muscles.

When they observed the movement of vesicles that contain dendritic proteins, Dr. Banker saw that they move into dendrites, but do not enter axons. To explain this remarkable observation, Dr. Banker hypothesized that the kinesin motors that move vesicles must be "smart"—that they are able to distinguish biochemical differences between axonal and dendritic microtubules and so can move preferentially to dendrites or axons. When the idea was originally proposed several years ago, it was quite speculative. However, in 2005, Dr. Banker's team developed methods to image the movements of the kinesin proteins themselves, when they are not attached to vesicles. This work confirmed the initial prediction that kinesins are smart. Some kinesins moved selectively along axonal microtubules, but avoided dendritic microtubules. The methods Dr. Banker's laboratory has developed to image protein transport also have great promise as assays to identify environmental (occupational) agents or genetic alterations that interfere with protein transport. These methods also could be used to screen for new drugs that might mitigate or correct these kinds of deficits in protein transport. (Silverman, et al., *Neuroscience*, 2005; 29, 173-180)

### Dominant Schwann Cell Role in Nerve Function and Recovery from Injury

All sights, sounds and sensation, as well as all movements of the body, are controlled by electrical impulses traveling along tiny nerve fibers, each about one-tenth the thickness of a human hair. After an injury, whether by insult, accident, or surgery, the fine features of the nerve must be fully regenerated to regain function. The ability of such thin nerve fibers to reliably carry information from one end to the other depends on a thin insulating layer of fat and protein that is rolled around the nerve cell, like gift wrapping paper on a cardboard tube. This material, called myelin, is created at about the time of birth by a special cell called a Schwann cell. Unrolled, the Schwann cell would look a bit like a very thin pancake and would cover more unbroken area than almost any cell in the body. How Schwann cells form myelin was described at the level of cell behavior many years ago. But little is known about what tells Schwann cells to form myelin in the manner required for normal function. Dr. Bruce Patton's research on a family of proteins called laminins has led to the discovery that they control Schwann cell proliferation and the decision to form myelin in the manner required for normal function. The laminin proteins form a covering sheet on the outer surface of the myelin, like the cellophane on a new roll of wrapping paper. Mice engineered to be missing the laminins had a normal set of nerves, but none of the nerve fibers were myelinated. The mutant Schwann cells were stuck in an immature state, unable to respond to signals to either proliferate or myelinate nerve fibers. Further studies revealed that laminins serve as a sort of molecular switch, which not only determines the ability of the cells to change after birth, but also ensures that cells proliferate in exactly the proportion needed for the size of the nerve. Dr. Patton is now deciphering molecular networks inside the cells that respond to this laminin switch, in hopes that clinical workers in the future can not only increase functional recovery during nerve regeneration after injury, but possibly reduce the extent of injury in the first place. Dr. Patton's original report can be found at [www.jcb.org/cgi/content/abstract/168/4/655](http://www.jcb.org/cgi/content/abstract/168/4/655).

## Chronic Disease and Working Safely

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Chronic disease takes a significant toll on our workforce just as it does in the broader community. CROET research seeks to discover causes of chronic diseases that are produced or exacerbated by workplace factors and identifies processes or procedures that can prevent or ameliorate those diseases and improve workplace safety.

### Model of Metabolic Syndrome in Obesity

The growing epidemic of human obesity is estimated to affect more than 60 million adult Americans, with secondary consequences including, but not limited to, decreased job performance, increased medical costs, decreased life span, non-alcohol-induced fatty liver disease, increased cardiovascular disease, and an increased incidence of stroke and type 2 diabetes. A majority of the obese population (more than 45 million Americans) has a combination of at least four of these diseases, collectively known as the Metabolic Syndrome. The underlying cause of these diseases is believed to be a combination of genetic susceptibility and chemical stressors, including exposure to pro-oxidant chemicals. Recently, Dr. Stephen Lloyd and his group have created genetically modified mice that are unable to repair certain types of oxidative DNA damage, and discovered that these mice develop symptoms consistent with all the defining hallmarks of the Metabolic Syndrome: severe obesity, disruptions in blood lipids, insulin resistance, and hyperleptinemia. Oxidative damage is believed to underlie some occupational disorders as well as diseases affecting broad segments of our population. The outcome of these investigations will be to provide a working model of the Metabolic Syndrome with which to design and test effective human therapies. By reducing the incidence or severity of disease associated with obesity, a healthier and more productive workforce can be realized.

### Neurodegeneration: *Drosophila*, a Model Test System

Dr. Doris Kretschmar uses the fruit fly, *Drosophila melanogaster*, to study basic mechanisms of neurodegeneration that are known to occur in occupational (e.g., chronic solvent exposure) and other diseases, including Alzheimer's disease. A key factor in Alzheimer's disease is the production, within the central nervous system, of small protein fragments called A $\beta$ , which are the major component of the amyloid plaques found in the brains of Alzheimer's patients. A $\beta$  is known to be produced by enzymatic cleavage of a larger protein called Amyloid Precursor Protein; therefore, if a drug can be developed to inhibit the enzymes involved in this processing step, it may be possible to treat Alzheimer's disease. However, besides A $\beta$ , three more protein fragments are produced by these enzymatic cleavage events. The Kretschmar laboratory is using *Drosophila* as an easily manipulated experimental animal model to study these fragments because they have shown that the pathogenic functions of A $\beta$ , including plaque formation and neuronal cell death, are the same as in human disease. An understanding of the function of the other Amyloid Precursor Protein fragments might aid the design of therapeutic drugs that have fewer adverse side effects than currently used drugs. Moreover, changes in the cleavage pattern as occurs in Alzheimer's disease might disrupt functions mediated by these other fragments, an effect that may also contribute to the disease. Although most cases of Alzheimer's disease are thought to be sporadic, several environmental and occupational agents have been described as risk factors. The *Drosophila* model can now be used to study the effects of such factors. By gaining a more complete understanding of the mechanisms of neurodegeneration in the fruit fly, it will be possible to transfer that knowledge from insects to vertebrates, to develop a fuller understanding of processes involved in a variety of human neurodegenerative diseases, including occupational diseases. More information about Dr. Kretschmar's work with fruit flies can be found in the CROET Newsletter, Volume 14, No. 2 (2006), located at [www.ohsu.edu/croet/about/pubs.cfm](http://www.ohsu.edu/croet/about/pubs.cfm).

### Mechanisms Underlying Chronic Health Effects of Organic Solvents are Illuminated

Organic solvents are valuable chemicals with a multitude of uses in a variety of industry sectors. While many are considered safe, a few solvents have the potential to cause neurological disease. Identifying the bad actors, and the reasons for their neurotoxicity, continues to be an important area of investigation in the laboratories of Dr. Peter Spencer and Dr. Mohammad Sabri. Previously reported studies revealed that both straight chain (aliphatic) and ring-structure (aromatic) solvents have neurotoxic potential if their metabolites possess chemical side chains with a particular (gamma-diketone) structure. Advanced methods of protein and gene analysis (toxicogenomics, *see below*), in combination with mass spectrometry, are being applied to understand why these chemicals are problematic and how they attack the nervous system. Drs. Spencer and Sabri demonstrated that the neurotoxicity of these solvents is directly related to a variety of specific chemical and physical characteristics of proteins, such that proteins in the nervous system are differentially susceptible to damage from the solvent metabolites. They also found that the loss of neuroproteins is accompanied by changes in gene expression that precede the onset of pathological changes in nerve fibers that underlie the appearance of neurological disease. This is hoped to lead to an understanding of how to predict which organic solvents have the potential to cause neurotoxicity and which are safe to use in the workplace.

### Publication in *Nature Methods* Sets Standards for the Practice of Toxicogenomics, a Leading-edge Research Method to Assess Impacts of Stressors on Gene Expression and Its Relationship with Health and Disease

Toxicogenomics is a powerful method to analyze the response of biological systems to changes induced by chemicals, drugs, trauma, and other agents that cause disease and injury. Tens of thousands of genes are simultaneously interrogated to determine whether and how gene expression has been changed from the normal state. The resulting mass of data is interpreted with software that reveals alterations in molecular networks that

correlate with abnormal function or a disease state. The reproducibility of this new technique was examined by a CROET investigative team, part of a prestigious Toxicogenomics Research Consortium (TRC) funded by the National Institutes of Environmental Health Sciences (NIEHS). CROET at OHSU carried out experiments conjointly with TRC members at NIEHS, MIT, Fred Hutchinson Cancer Research Center, University of Washington, Duke University and University of North Carolina. The collaborative research effort revealed critical elements, including the quality and stability of the microarray platform, the precision of the experimental procedures, anchoring gene expression data to established biological landmarks, and the power of innovative biostatistical methods to extract information from the mountain of data that results from toxicogenomics experiments. In sum, these studies show the challenges as well as the strengths of toxicogenomics as a tool to probe and increase understanding of health and disease. (Bammler, et al., *Nature Methods*, 2005; 2: 351-356).

## Reducing the Risk of Prostate Cancer

Prostate cancer is the second leading cause of cancer deaths among U.S. men, and there are currently few options for prevention. Prostate cancer is most likely to be diagnosed in men over the age of 50, and many men are diagnosed with this potentially debilitating disease while still an active part of the workforce. While treatable if caught early, surgery is highly invasive, and five-year survival rates for recurrent disease remain quite low. Dr. Jackilen Shannon has found that men who have been prescribed statins to treat high cholesterol have a 65 percent lower risk of developing prostate cancer than men who have taken no statins at all. When the men were analyzed separately according to the severity of their cancer at diagnosis, the association between statin use and prostate cancer prevention was found to be strongest for the more severe cases. One hundred prostate cancer patients were recruited into the study. They had been referred for prostate biopsies at the Portland Veterans Affairs Medical Center (PVAMC) because of elevated prostate-specific antigen (PSA) levels, or abnormal prostate exams. Statin use among these men was recorded and compared to the use of statins among a control group of 202 PVAMC patients whose PSA levels had remained unchanged for a year. Statin use was grouped by duration and intensity of use: those who had used statins for the longest period (more than 2.8 years) and at higher doses (average daily dose of more than 40mg/day) reduced their risk the most. (Shannon et al., *American Journal of Epidemiology*, 2005; 162: 318-325)

## Integrity of DNA (DNA damage, genetic alterations, and disease)

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Human health and risk for disease ultimately depend on the integrity of our DNA, the genetic material that provides the body's blueprint for manufacturing proteins that carry out the function of cells and organs. Aberrant forms of DNA can produce inherited diseases, and changes in DNA during life are believed to trigger cancer and many other chronic diseases. Such changes can result from exposure to certain chemicals found in the workplace and others in the diet and medications. Two broad types of DNA changes are recognized: DNA damage and DNA silencing.

### Persistence of DNA Damage After a Single Exposure to Ionizing Radiation

DNA damage represents one of the earliest steps in the development of cancer because such damage can lead to mutations in genes that function to prevent cancer. Mutation is defined as changes in DNA structure that alter the ability of a gene to make a protein. Because proteins constitute the basic functional machinery of cells, the resultant change in the amount or activity of a protein (after DNA mutation) can fundamentally alter cellular behavior. Ionizing radiation, such as the common X-ray or ultraviolet radiation from sunlight, causes two types of DNA damage: (1) breaks in the DNA strand and (2) damage to nucleotides, the building blocks of DNA. Cells have a variety of mechanisms to repair DNA damage and hence avoid the induction of a harmful mutation. Dr. Mitchell Turker's laboratory is asking whether DNA damage caused by exposure to ionizing radiation persists in tissues or whether the damage is fixed by DNA repair mechanisms. Some mouse tissues are exposed to ionizing radiation while others are shielded from exposure. DNA damage is assessed in tissues of the irradiated mice by examining chromosome structure (chromosomes contain the DNA strands) long after treatment. The results demonstrated that specific types of chromosome abnormalities caused by ionizing radiation persist for two years and at levels that were essentially the same as those observed one to four weeks after exposure. Although the ionizing radiation dosages used for this experiment were far higher than those employed in diagnostic procedures, these results support the concept that such procedures should be limited only to those necessary for medical evaluations. While we have learned a great deal about acute exposures, the effects of long-term exposure to low doses of ionizing radiation is still an open question.

### Mutations Increase with Age in Mouse Tissues

The greatest risk factor for cancer is age, and cancer is more common in older than in younger persons. This is believed to reflect basic changes in cell structure and function as people get older, but the exact nature of these changes remains to be determined. One type of cellular change that is important in cancer is gene mutation, which occurs when the DNA sequence is altered and expression of genes required to prevent cancer is lost. Dr. Turker examined the frequency of mutations most commonly found in cancer cells of two cell types from mice ranging in age from 6 months to 36 months (laboratory mice rarely live past 40 months of age). The cell types examined were those found in connective tissue and kidney epithelial cells. Most tumors that increase with age arise from epithelial cells. The results of Dr. Turker's experiments demonstrated a steady increase in the frequency of mutations for the kidney cells as a function of age, which was higher at all ages in the female mice. Interestingly, female mice do not live as long as male mice in the strain that was used for this study. For the connective tissue cells, an age-related increase in mutations was only observed for female mice and only in the oldest females. These results demonstrate that mutations with relevance for cancer increase with age mostly in epithelial cell types and suggest that this cell-type-specific increase plays an important role in cancers that arise in older individuals.

## Business Spinoffs

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The federal government, the State of Oregon, and OHSU encourage the translation of research findings into immediate real-world benefits to society. Often that is in the form of commercial products that generate income for OHSU, part of which returns directly to the laboratory where the idea for the product was generated. This is a natural outgrowth of CROET's legislative mandate since many of its research activities are aimed at solving workplace problems, either through prevention or treatment. Two corporate spinoffs and one for-fee service operating within CROET have achieved significant milestones in 2004-2005. They are described below.

### Restoration Genetics, Inc.

The occurrence of skin cancer is rapidly increasing, affecting more than 1 million people in the United States annually. Sunlight exposure produces DNA damage or lesions, and they in turn can produce cancer. Human cells have only one mechanism to repair these DNA lesions, whereas lower organisms possess multiple pathways for protection against the adverse effects of sunlight exposure. In order to implement proactive strategies to prevent skin cancer, Dr. Amanda McCullough and Dr. Stephen Lloyd have discovered, characterized and patented multiple DNA-repair enzymes that possess activities that can initiate a second DNA-repair pathway in human cells. Cell-based studies have demonstrated that repair of sunlight-induced DNA damage can be improved 100 fold over that of non-treated cells. Based on these patented technologies, Drs. McCullough and Lloyd co-founded a start-up biotechnology research and development company, Restoration Genetics, Inc., in August 2004. In 2005, the McCullough and Lloyd laboratories were awarded a Springboard Grant from OHSU to facilitate start-up operations for the company. Additionally, a BioScience Innovation Fund Grant from OHSU was awarded to provide funds to demonstrate the feasibility of incorporating these enzymes in an active form in skin-specific vesicles that, upon topical application to skin, will enhance repair of sunlight-induced DNA damage. What this promises is a post-sunburn application that can reverse the damage done to the DNA in the skin. These technologies have the potential to repair the most harmful damage caused by sunlight exposure. By restoring the cellular DNA to its original state, mutations that could lead to cancer are prevented and the skin's immune responses are restored. It is envisioned that this technology could be used either pre- or post-sunlight exposure, resulting in improved skin health.

### Northwest Education Training and Assessment, LLC (NwETA)

Computer-based training is efficient but developed largely by and for well-educated segments of the working population. In 1999-2001, Dr. Kent Anger and Dr. Diane Rohlman developed cTRAIN, a computer-based training software aimed at training populations that had limited or no experience with computers. In 2005, the cTRAIN software was licensed by OHSU to Northwest Education Training and Assessment ([www.nweta.com](http://www.nweta.com)), an OHSU spin-off company formed by Dr. Anger, Dr. Rohlman and other colleagues. The goal of the company is to commercialize cTRAIN and use the proceeds from sales to evolve the software in order to maintain and enhance its utility and competitiveness with other training software. The software presents training created in Dr. Anger's laboratory, but it also has an editing tool in which new content topics can be created. The cTRAIN computer-based training program received seed funding from an OR-OSHA grant to the Painter's District Council. Through this grant, Dr. Anger and Mr. Kirkpatrick developed training content on respiratory protection that is still in use at the Painter's District Council Training Center today. Federal grants further supported the development of content on slip-and-fall safety in food service operations, ladder safety in agriculture, ergonomic issues in dry wall finishing, hazard communication, Worker Protection Standard for agricultural workers, and a variety of training content programs for vineyards. This led to a small business grant to NwETA from the National Institute of Environmental Health Sciences and a cooperative agreement from the National Institute for Occupational Safety and Health (NIOSH) to develop training content programs for vineyards in collaboration with Leda Garside, RN, BSD, of Tuality Healthcare ;Salud! Services. NwETA's goal is to bring the efficiencies and advantages of computer-based training to every working person, including those in the workforce with limited or no education.

### Chemical Risk Information Service

OSHA regulations require employers to maintain Material Safety Data Sheets (MSDS) for hazardous chemicals used in their workplace. This often proves to be a difficult record-keeping task, and it can be burdensome to ensure that employees have quick access to health and safety information in the workplace when they need it. Since 1998, CROET's Chemical Risk Information Service, directed by Dr. Gregory Higgins, has helped a growing number of local and international industries manage and distribute chemical safety information through its computer-based MSDS management system. CROET's working relationship with the Oregon Poison Center also ensures that employees covered by the program have ready access to medical information in the event of exposure. During 2004-2005, the Chemical Risk Information Service provided MSDS management services to more than 35 municipal, construction, and service companies, most of which are Oregon-based. CROET is currently focused on upgrading the database system and improving client websites for MSDS management. All database files and websites were relocated from CROET's local server to OHSU's main server bank, which improved the security and reliability of the service. We also began development of improved search codes for clients to retrieve MSDSs, so that they can begin to search not only by product name, but also by key location parameters at their facilities. This change allows clients to use CROET's system as an inventory control mechanism, as well as a source for MSDSs. CROET continues to provide expert MSDS management service at a reasonable cost which is attractive to both small and large organizations.



## CROET Expenditures: Fiscal Year 2003-2004

Workers' Compensation Funded Expenditures	
<b>Salaries</b>	
Salaries – research (19% of all salaries)	\$920,933
Salaries – outreach (6% of all salaries)	273,894
Salaries – education (3% of all salaries)	130,961
Salaries – administration (6% of all salaries)	322,094
Salaries – core services <sup>1</sup> (3% of all salaries)	134,241
<b>Supporting Services (includes cores)</b>	
Supplies and equipment	853,368
Miscellaneous support <sup>2</sup>	213,342
<b>Outreach and Education</b>	
Services, supplies and equipment	347,795
<b>Other Expenses</b>	
Bond principal & interest	353,481
OHSU administrative charges	123,608
<b>Total</b>	<b>\$3,673,717</b>

Federal and Other Grant Funded Expenditures	
<b>Salaries</b>	
Salaries – research (54% of all salaries)	\$2,686,218
Salaries – outreach	386
Salaries – education (1% of all salaries)	38,049
Salaries – administration (6% of all salaries)	336,034
Salaries – core services (2% of all salaries)	105,973
<b>Supplies and equipment</b>	
Laboratory supplies, animal costs, human subjects, equipment and other expenses	3,200,189
<b>Other Expenses</b>	
Building operations & maintenance	602,745
<b>Total</b>	<b>\$6,969,594</b>

## Programs: Fiscal Year 2003-2004

	Amount paid by W/C	Amount paid by grants	Total cost
<b>Outreach and Education</b>			
Information dissemination (e.g., TIC <sup>3</sup> , web site, newsletters, brochures)	\$551,893	\$14,193	\$566,086
Education & training programs (professional & para-professional)	212,446	358,760	571,206
Chemical risk information service	(11,687)	0	(11,687)
<b>Basic and Applied Research</b>			
Factors that affect workplace performance	143,525	1,447,262	1,590,787
Damage and repair of the nervous system and muscles	473,072	772,747	1,245,819
Occupational/environmental exposures and their consequences	411,062	2,427,190	2,838,252
DNA damage, genetic alterations & disease	486,951	813,371	1,300,322
Core services support <sup>1</sup>	134,239	115,595	249,834
<b>Non-program-specific expenses<sup>4</sup></b>	<b>1,272,216</b>	<b>1,020,476</b>	<b>2,292,692</b>
<b>Total Expenses</b>	<b>\$3,673,717</b>	<b>\$6,969,594</b>	<b>\$10,643,311</b>

<sup>1</sup> Core services - centralized graphics, statistics, imaging, tissue culture and morphology (pathology)

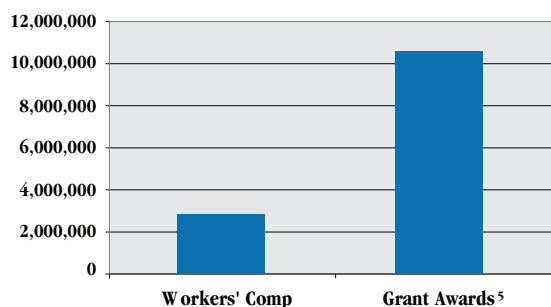
<sup>2</sup> e.g., office supplies, equipment maintenance and repair, phone rental and line charges

<sup>3</sup> Toxicology Information Center

<sup>4</sup> Includes supporting services, administrative salaries, bond principal and interest, OHSU administrative charges, building operation and maintenance

<sup>5</sup> Timing of faculty arriving and leaving OHSU resulted in inflated award figures in this period.

**Funding Sources: Income and Awards 2003-2004**



## CROET Expenditures: Fiscal Year 2004-2005

Workers' Compensation Funded Expenditures	
<b>Salaries</b>	
Salaries – research (13% of all salaries)	\$680,259
Salaries – outreach (7% of all salaries)	361,944
Salaries – education (2% of all salaries)	135,678
Salaries – administration (5% of all salaries)	296,183
Salaries – core services <sup>1</sup> (1% of all salaries)	56,432
<b>Supporting Services (includes cores)</b>	
Supplies and equipment	338,345
Miscellaneous support <sup>2</sup>	84,586
<b>Outreach and Education</b>	
Services, supplies and equipment	152,451
<b>Other Expenses</b>	
Bond principal & interest	353,481
OHSU administrative charges	625,000
<b>Total</b>	<b>\$3,084,359</b>

Federal and Other Grant Funded Expenditures	
<b>Salaries</b>	
Salaries – research (61% of all salaries)	\$3,290,789
Salaries – outreach	4,828
Salaries – education (1% of all salaries)	61,781
Salaries – administration (7% of all salaries)	362,908
Salaries – core services (3% of all salaries)	180,840
<b>Supplies and equipment</b>	
Laboratory supplies, animal costs, human subjects, equipment and other expenses	2,457,767
<b>Other Expenses</b>	
Building operations & maintenance	576,877
<b>Total</b>	<b>\$6,935,789</b>

## Programs: Fiscal Year 2004-2005

	Amount paid by W/C	Amount paid by grants	Total cost
<b>Outreach and Education</b>			
Information dissemination (e.g., TIC <sup>3</sup> , web site, newsletters, brochures)	\$511,064	\$18,213	\$529,277
Education & training programs (professional & para-professional)	158,578	360,706	519,284
Chemical risk information service	(19,569)	0	(19,569)
<b>Basic and Applied Research</b>			
Factors that affect workplace performance	165,622	994,832	1,160,454
Damage and repair of the nervous system and muscle	348,511	822,493	1,171,004
Occupational/environmental exposures and their consequences	301,324	2,243,321	2,544,645
DNA damage, genetic alterations & disease	132,293	1,428,160	1,560,453
Core services support <sup>1</sup>	14,750	203,402	218,152
<b>Non-program-specific expenses<sup>4</sup></b>	<b>1,471,786</b>	<b>864,663</b>	<b>2,336,449</b>
<b>Total Expenses</b>	<b>\$3,084,359</b>	<b>\$6,935,790</b>	<b>\$10,020,149</b>

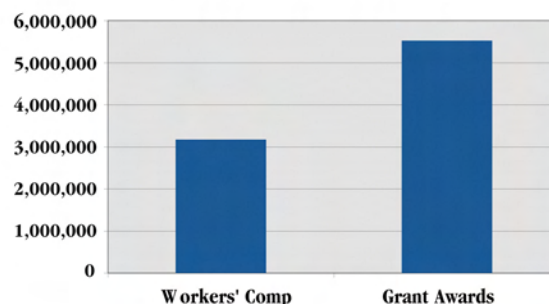
<sup>1</sup> Core services - centralized graphics, statistics, imaging, tissue culture and morphology (pathology)

<sup>2</sup> e.g., office supplies, equipment maintenance and repair, phone rental and line charges

<sup>3</sup> Toxicology Information Center

<sup>4</sup> Includes supporting services, administrative salaries, bond principal and interest, OHSU administrative charges, building operation and maintenance

**Funding Sources: Income and Awards 2004-2005**





# CROET

The Center for Research on Occupational and Environmental Toxicology (CROET) conducts research, trains health professionals, provides consultation, and offers the public information on hazardous chemicals and their health effects. CROET includes more than 100 scientists and research staff exploring a range of questions relating to prevention of injury and disease – and promotion of health – in the workforce of Oregon and beyond. CROET's Toxicology Information Center (TIC) is staffed to answer Oregonians' questions about chemical and other occupational exposures, and the Center's web site makes health and safety information continuously available.

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For additional copies of this report, call CROET at the numbers listed above or visit [www.ohsu.edu/croet](http://www.ohsu.edu/croet) and click on "About."

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### Associate Director and Senior Scientist

W. Kent Anger, PhD

### Assistant Director for Operations

Gregory Higgins, PhD

### Assistant Director for Business Affairs

Janice Stewart, BS

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Gary Banker, PhD  
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Doris Kretzschmar, PhD  
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Pamela Lein, PhD  
R. Stephen Lloyd, PhD  
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D. Gary Rischitelli, MD, JD, MPH, FACOEM  
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Terry Hammond, MPH  
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Robert Kayton, PhD

## FRONT COVER

### Top Photo

A mechanical log loader stacks logs at an Oregon logging site (*photo by OR-FACE investigator Larry Smith, taken during an investigation of a fatal incident*).

### Middle Photo

CROET summer student poster presentation to the Center (*photo by Dan Austin*).

### Bottom Photo

Spinal cord nerve cells with grossly swollen axonal processes [a] caused by repeated exposure to an organic solvent breakdown product that causes severe limb weakness. (*photomicrograph by Robert Kayton, PhD. Magnification ~100X*).

## BACK COVER

CROET engages in research to identify and prevent illnesses and injuries in the workforce. Although we blaze a new trail, we are not the first to walk in these woods. For centuries, workers and physicians have sought to clarify the relationships between various exposures and disease. Listed on the back cover are descriptions of occupational disorders named by those afflicted or by their caregivers.

Sihyun Kim, PhD  
Louise Kling, MS  
Lena Kolotushkina, PhD  
Michael La Flamme, PhD  
Michael Lasarev, MS  
Irina Minko, PhD  
Mykhaylo Moldavan, PhD  
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