

C R O E T

Center for
Research on
Occupational and
Environmental
Toxicology



NEWSLETTER

CROET Scientists Developing New Preventative for Sunlight- Induced Skin Cancer

INSIDE

*CROET's Dan Austin Speaks
at BIOCOMM 2005.....3*

*CROET Co-Sponsors Inter-
national Symposium4*

*CROET Hosts Chinese
Scientists4*

*Hazards of Hydrofluoric
Acid5*

*CROET Co-Sponsors OS&H
Conference.....6*

Contact Us7

Outreach8

It's a fact: there is no such thing as healthy exposure to ultraviolet (UV) radiation, yet every day millions of Americans are exposed occupationally to UV light from the sun and other sources. Whether you work in outdoor occupations such as construction, agriculture, the fishing industry or operate electric arc welding equipment, UV light exposure damages DNA and increases your risk for skin cancer.

CROET scientists Stephen Lloyd and Amanda McCullough are interested in DNA mutation and the mechanisms cells use to repair DNA damage induced by environmental stresses. It is through basic research into the biomolecular mechanisms of UV-induced DNA mutation and repair that they have devised and are now developing a novel strategy for preventing UV light-induced skin cancer. This important research was reported in the September 9, 2005 edition of the Portland Business Journal (Portland.bizjournals.com).

Skin cancer incidence is increasing and is responsible for half of all new cancers in the



United States, over one million cases a year. Most of these, ninety-six percent, are non-melanoma skin cancers derived from basal cells and squamous epithelial cells. While skin cancer risk can be reduced through the use of UV-blocking skin creams, shades and protective clothing, such protection is rarely used in a proper and consistent manner. Drs. McCullough and Lloyd hope to provide an additional level of protection, but to understand their skin cancer prevention strategy, we must first understand how it is that UV radiation alters DNA and how our cells repair this damage.

When UV light interacts with DNA, its energy creates damaging chemical cross-linkages between adjacent DNA bases, forming what are called pyrimidine dimers (see figure 1, number 1). Pyrimidine dimers interfere with vital coding, regulatory and replication functions of the cell's DNA, and if such mutations are allowed to accumulate within critical genes and/or gene regulatory elements, then skin cells may become cancerous.

Fortunately, we have evolved a variety of DNA repair enzymes that battle a constant onslaught of DNA mutating events, which is good — however, humans and other mammals have only one DNA repair system, called nucleotide excision repair (NER), for removing pyrimidine dimers. NER is a complicated and inefficient UV damage repair process that removes long

stretches of DNA surrounding pyrimidine dimers and replaces them with normal DNA. Bacteria, on the other hand, have evolved a DNA repair system called base excision repair (BER), which uses the

enzyme pyrimidine dimer glycosylase to remove only the pyrimidine dimer. Drs. Lloyd and McCullough reasoned that it may be possible to augment the mammalian NER system by supplying skin cells with the bacterial BER enzyme, which could be applied in a lotion to the skin (see figure 1, number 2). Once the bacterial enzyme has

removed the pyrimidine dimer, other innate cellular processes are engaged to replace the missing DNA bases and restore normal DNA architecture (figure 1, numbers 3 & 4). Thus, instead of one DNA repair pathway, we would in effect have two levels of protection against UV light-induced DNA mutation.

While this strategy looks simple, its application is not straightforward. The problem is in getting the enzyme through the cell's outer membrane and into its nucleus where the DNA is located. This problem was partially solved by encasing the enzyme in lipid globules called liposomes, which readily

pass through a cell's outer lipid membrane — but getting PDG into a cell's nucleus required tagging the enzyme by attaching a targeting protein onto the molecule. Targeted PDG should now be recognized by the cell and transported into the nucleus (see figure 2).

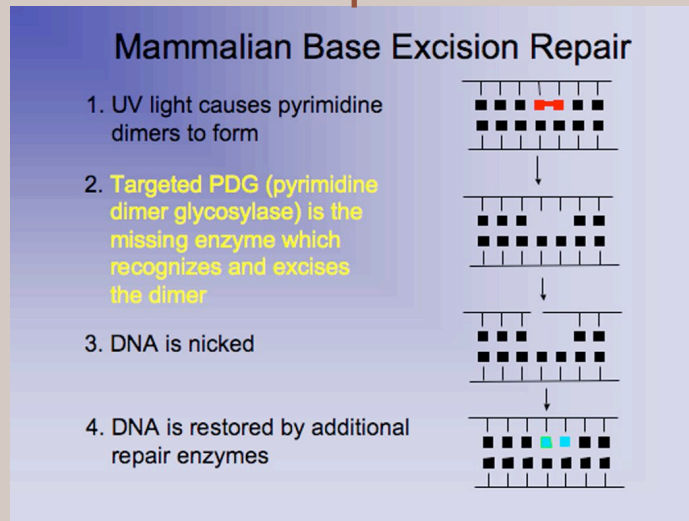


Figure 1

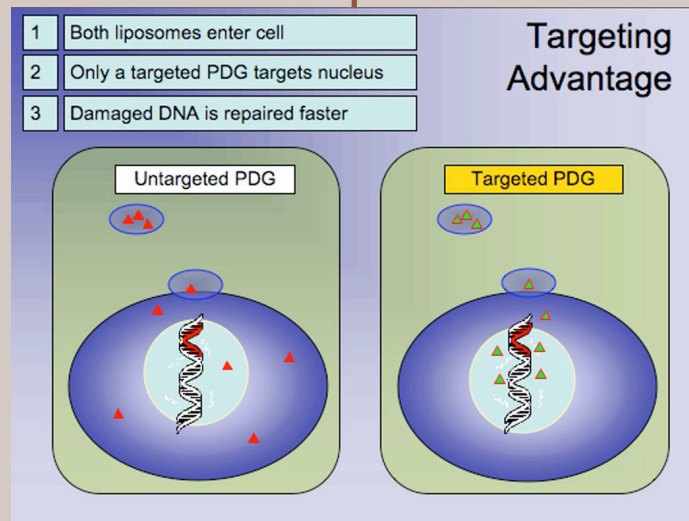


Figure 2

With these modifications, targeted PDG should repair a cell's UV-damaged DNA, but does it work? The short answer is yes — at least in the Petri dish. Cultured cells irradiated with UV light and then treated with targeted PDG showed a high level of DNA repair as compared to UV-exposed, untreated controls (see figure 3).

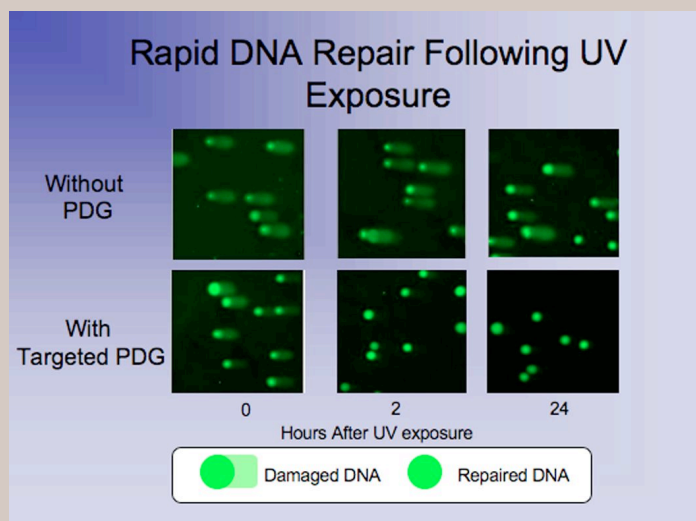


Figure 3

So what's next? Drs. Lloyd and McCullough must now conduct further proof of concept research before clinical trials of a cancer-preventative cream can begin. If all goes smoothly, a marketable product may be possible in ten or so years. While this may seem like a long time, the long-term goal of preventing or delaying UV light-induced skin cancers due to unavoidable exposure makes it all worth the effort. Moreover, targeted PDG may provide lifesaving benefits to populations with increased risks of aggressive skin carcinomas due to genetic or other predisposition.

People often ask the question: how do I benefit from basic research being conducted at CROET? Dr. Lloyd and Dr. McCullough are providing a loud and clear answer to this question. Without looking closely at the minute structure and function of the cell, a new and exciting technology for preventing UV light-induced skin cancers would be denied to the working people of Oregon and beyond. CROET scientists are devoted to improving the lives of all working Oregonians.

CROET's Dan Austin Speaks at 2005 BioCommunications Association Meeting

Portland was host to BIOCOMM 2005, the seventy-fifth annual meeting of the BioCommunications Association, a group dedicated to the advancement of scientific and medical imaging and information technology.



Speakers from all across the nation presented valuable information on a variety of subjects, including electronic submission of papers, digital wound imaging protocols and photographic imaging of the eye, among others. CROET's Dan Austin presented a talk titled "Authoring DVDs in the Modern World", which examined the different worldwide formats for DVDs, movies and video and discussed some of the authoring programs available for use on PC and MAC operating systems. Authoring of DVDs is becoming more commonplace as technology advances and equipment costs decrease. However, the many DVD formats available makes creating compatible DVDs a risky and confusing undertaking. Dan's presentation helped to eliminate much of that confusion. Dan has worked in research for more than 25 years, the first 15 of which were spent in biochemistry, histology and neurobiology. In 1994, he created the graphics core at CROET, which serves the science communication needs of faculty and researchers, producing figures and movies for publications, presentations and meetings, as well as developing new communications techniques.

CROET Co-Sponsors International Symposium on Neurosciences in Central Africa

CROET, Oregon Health & Science University and Portland-based Third World Medical Research Foundation co-sponsored the Second International Symposium on Neurosciences in Central Africa, held November 8-10, 2004 at the Hall of Notre Dame de Fatima in Kinshasa, DR Congo. The theme of this year's meeting, titled "Neurosciences, Mental Health and Development", addressed basic and crucial issues surrounding the development of clinical neurosciences and related medical fields in Central Africa.

The three-day symposium was host to more than 150 people from various backgrounds, including

neuroscientists, medical practitioners, journalists, residents and medical students. CROET investigator Daniel D. Tshala-Katumbay, MD, PhD, played a central role in planning the conference, was a special

guest and chaired a minisymposium on neurotoxicity and neuroscience research. Speakers attending the mini-symposium talked about their research on various subjects, including free radicals in sport and the use of cannabis, and about their clinical experience with neurological diseases such as lead poisoning and Konzo, from dietary dependency on cassava root. Dr. Tshala-Katumbay concluded the mini-symposium with a talk in which he emphasized the necessity for establishing communications between local and regional teams working to eliminate neurotoxic disease in Africa and researchers from around the world with expertise on such diseases.



Dr. Tshala-Katumbay

At the conclusion of the symposium, Dr. Tshala-Katumbay was given the opportunity to deliver a short speech in which he thanked those responsible for planning the meeting and those who are most intimately involved in developing the neurosciences in Central Africa.

CROET Welcomes Visiting Scientists from China

CROET hosted two distinguished scientists from the Peoples Republic of China.

Xiaojun Zhou, MD, PhD, is Director of the Nanobiotechnology and Membrane Biology Institute at Sichuan University, Chengdu, P.R. China. Professor Zhou received his MA in biochemistry and molecular biology from the University of California at Santa Barbara and his PhD in biological chemistry from the UCLA School of Medicine. Prior to his current position in China, Dr. Zhou served as Manager of the Molecular Self-Assembly Laboratory at the Massachusetts Institute of Technology. Dr. Zhou has research interests in neurobiology and protein chemistry.

Qiao Niu, MD, PhD, is Professor of Occupational Health and Toxicology, Director of the Occupational Health department and Dean of the School of Public Health at Shanxi Medical University, Taiyuan, P.R. China. He received his MD from the School of Public Health, Shanxi Medical College, and his PhD from the Department of Occupational and Environmental Health at Fudan University in Shanghai. Professor Niu has research interests in the neurotoxicology and immuno-toxicology of metals and solvents.

The scientist's visit is the result of efforts by CROET's Director, Peter Spencer, to foster collaborations between this center and scientists from around the world who share expertise in issues related to occupational safety and health.

The Hazard of Hydrofluoric Acid

Hydrogen fluoride is a colorless gas that is produced when sulfuric acid is reacted with fluorospar (calcium fluoride) in a heated kiln. It is then purified and condensed into the liquid form known as hydrofluoric acid (HF). HF has a variety of industrial uses, including glass etching, metal cleaning, petrochemical manufacturing, and semiconductor production. It is also present in some home rust removers and other household products. Because of its wide use, a relatively large population of workers is at potential risk for exposure to HF.

Although HF is one of the most corrosive and hazardous of inorganic acids and will fume at concentrations above 40 to 50%, it is actually classified as a weak acid due to the extremely high binding affinity that exists between hydrogen and fluoride — they do not readily dissociate in water. Thus, when compared to hydrochloric acid, a HF solution of the same concentration contains approximately one thousand times less free hydrogen ion and is therefore much less corrosive. In fact, HF does not readily produce acid burns at concentrations less than about 20-50%. What really makes HF a particularly hazardous substance is that it not only causes corrosive acid burns at higher concentrations due to free hydrogen ions, but also causes fluoride-induced chemical burns at both high and low concentrations.

Dilute solutions of HF are a particularly insidious hazard because tissue injury may not be detected until hours after an exposure. Dilute HF readily penetrates intact skin and can travel deeply into tissues before dissociation and release of damaging fluoride ions occurs (hydrogen ion at low concentrations may be harmlessly neutralized). Because of this, burns to the fingers and nail beds

may leave the overlying fingernails intact, and severe pain with little surface abnormality may occur. Symptoms can be delayed as long as one to eight hours after skin contact with a 20 to 50% HF solution, and up to 24 hours or longer after exposure to as little as 2% HF. The initial signs of an HF burn include severe throbbing pain followed by redness, edema and blistering of the skin; higher concentrations (50% or higher) produce immediate pain and whitish blanching of the skin. Left untreated, severe damage and loss of deeper tissues, including muscle and bone, may occur. And unlike other acids where hydrogen ion is rapidly neutralized in the tissues, fluoride will continue to damage or destroy tissues for days if left untreated.

One other hazard posed by HF is that burns covering an area larger than about 25 square inches (about the size of a grapefruit) may also result in serious systemic toxicity. Fluoride forms insoluble complexes with calcium and magnesium in the body, which can markedly lower the level of calcium (hypocalcemia) and magnesium (hypomagnesemia) and elevate potassium (hyperkalemia) in the blood. Such a disturbance in ion balance can severely alter a variety of cellular metabolic functions, resulting in heart arrhythmias, cardiac arrest and death.

Prevention of HF exposure

Any workplace that uses HF should implement strict rules for its storage and handling and ensure that all potentially exposed personnel are well trained in HF safety policies. Protective equipment and clothing should be provided and their use strictly required. These include, at a minimum: coveralls with long sleeves that are made of impervious material, face shields, hard hats, PVC

or neoprene long-sleeved gloves, and rubber safety shoes with PVC, neoprene or composition soles. Moreover, a complete continuing education program on safe work practices and the use of clothing and equipment, including respirators, should be mandated for all employees at risk of exposure to HF.

First aid for HF Exposure

This article only addresses HF exposures that involve contact with skin; eye, inhalation and ingestion are also potential routes for HF exposure. It is beyond the scope of this article to attempt to comprehensively address first aid treatment of HF exposures. The primary factor to be aware of is that speed is of the essence: exposed individuals should be removed from the area immediately and treatment started within seconds. This might include having calcium gluconate first aid gel (or similar treatment to bind and neutralize harmful fluoride ions) on hand for immediate use in the event of an exposure. Thus, it is very important for the workplace to have a written first aid plan that all workers are intimately familiar with before work with HF is undertaken. This plan should require that all personnel be familiar with first aid procedures, that all potential exposures are treated, and that a physician must be seen as soon as possible, no matter how minor the exposure. And, to be completely prepared, it would be advantageous for workplace safety personnel to communicate and coordinate with local hospital emergency facilities so that they are adequately prepared for any exposure scenario that may arise.

For more comprehensive information about HF and other acids or bases, visit www.CROETweb.com and click on our new topic, “Acids and Bases”, under the Chemical Hazards heading.

CROET Co-Sponsors Occupational Safety and Health Conference

CROET and the department of Psychology at Portland State University (PSU) co-sponsored an occupational safety and health symposium titled “The Multidimensional Causes of Accidents and Injuries”, on November 18, 2005 at PSU. This popular symposium (as judged by the standing room-only crowd of attendees) examined workplace accidents and injuries, their causes and possible solutions from a variety of perspectives. After opening remarks by Drs. Leslie Hammer and Bob Sinclair of PSU’s department of Psychology, Oregon Nursing Association’s Lynda Enos, a nursing practices specialist and ergonomist, presented information about how workplace design can reduce accidents and injuries by optimizing worker efficiency and reducing the risk of human error. From a different perspective, Dr. George Paaanen’s presentation, “The Complexity of Hiring Safe Employees”, examined the use of psychological testing as a tool for hiring workers. In the afternoon, Jackie Nowell, of United Food and Commercial Workers International addressed causes of work-related injury from the labor perspective and Dr. John Austin, from Western Michigan University’s department of Psychology, described programs to reduce accidents. The information presented was enlightening and educational - even controversial - which stimulated questions and comments from conference attendees during the final speaker’s panel discussion, moderated by Bob Sinclair.

If you would like to know more about CROET-sponsored events, as well as new information updates on our website, please join our email list at www.croetweb.com

Center for **R**esearch on **O**ccupational and **E**nvironmental **T**oxicology

CROET, the Center for Research on Occupational and Environmental Toxicology at Oregon Health & Science University, conducts research, provides consultations and offers information on hazardous chemicals and their health effects. CROET's 100+ scientists and research staff explore a range of questions relating to health and the prevention of injury and disease in the workforce of Oregon and beyond. CROET's Toxicology Information Center is open to the public and is staffed to answer Oregonians' questions about hazardous substances in the workplace and elsewhere. CROET's Web site also provides answers to questions about industries found in Oregon through links on a series of pages devoted to industry-specific topics.

How to Contact Us

MAIL ADDRESS

CROET
Oregon Health & Science University
3181 SW Sam Jackson Park Rd, L606
Portland, OR 97239-3098

Web site

<http://www.ohsu.edu/croet/>

TELEPHONE

Main CROET number
(503) 494-4273
Facsimile
(503) 494-4278
Toxicology Information Center
(800) 457-8627

E-MAIL

Toxicology Information Center
croettic@ohsu.edu

Share your comments regarding this publication by calling (503) 494-2514, by e-mailing us at scottv@ohsu.edu or by faxing us at (503) 494-4278

Directors and Scientists

DIRECTOR AND SENIOR SCIENTIST

Peter S. Spencer, PhD, FRCPATH

ASSOCIATE DIRECTOR AND SENIOR SCIENTIST

W. Kent Anger, PhD

ASSISTANT DIRECTORS

Gregory Higgins, PhD
Janice Stewart, BS

FACULTY

Charles Allen, PhD
W. Kent Anger, PhD
Gary Banker, PhD
Bruce Gold, PhD
Anne Greenlee, PhD
Glen Kisby, PhD
Dennis Koop, PhD
Doris Kretzschmar, PhD
William Lambert, PhD
Pamela Lein, PhD
R. Stephen Lloyd, PhD
Amanda McCullough, PhD
Ryan Olson, PhD
Bruce Patton, PhD
D. Gary Rischitelli, MD, JD, MPH, FACOEM
Show-Ling Shyng, PhD
Peter S. Spencer, PhD, FRCPATH
Philippe Thuillier, PhD
Mitchell Turker, PhD

INVESTIGATORS

Gregory Higgins, PhD
Robert Irwin, MD, MPH
Stefanie Kaech Petrie, PhD
Irina Minko, PhD
Mohammad Sabri, PhD
Daniel D. Tshala-Katumbay, M.D., PhD

SCIENTIFIC STAFF

Ludovic Alvado, PhD
Daniel Austin, MS
Frederick Berman, DVM, PhD
Thomas Brudnicki, MS
Bendert deGraaf, MS
Karen Fujimoto, BS
Terry Hammond, MPH
Seyed Hashemi, MA, MS
Brenda Hoppe, MS
Robert Kayton, PhD
SiHyun Kim, PhD
Louise Kling, MS
Olena Kolotushkina, PhD
Michael LaFlamme, PhD
Mike Lasarev, MS
Xiaorong (Jerry) Li, PhD
Michelle Massoth, MA
Mykhaylo Moldavan, PhD
Dede Montgomery, MS, CIH
Valerie Palmer, BS
Diane Rohlman, PhD
Joan Rothlein, PhD
Bernard Sampo, PhD
Katia Carmine-Simmen, PhD
Liisa Tremere, PhD
Vladimir Vartanian, PhD
Feifei Yan, PhD
DongRen Yang, PhD
Xiaolin Yu, MS

OUTREACH

CROET will exhibit at the following conferences.

Bob Bryant Memorial Cascade Occupational Safety & Health Conference

Lane Community College Center for Meeting & Learning • Eugene, Oregon

March 8-10, 2006

Oregon Workers' Compensation Educational Conference

Portland Marriott Downtown • Portland, Oregon

May 15-16, 2006

HealthCare Ergonomics Conference

Oregon Convention Center • Portland, Oregon

June 26-29, 2006

Join our monthly E-mail list

Join CROET's e-mail list for monthly updates about additions to the CROET web site, news and upcoming events. To subscribe or read past updates, go to <http://www.croetweb.com/>

Oregon Health & Science University includes the Schools of Dentistry, Medicine, Nursing and Science and Engineering; OHSU Hospital; numerous primary care and specialty clinics; multiple research institutes and several outreach and public service units. OHSU is an equal opportunity, affirmative action institution.

Oregon Health & Science University
CROET, the Center for Research on
Occupational and Environmental Toxicology
3181 SW Sam Jackson Park Rd., L606
Portland, OR 97239-3098



Non-Profit Org.
U.S. Postage
PAID
Permit No. 722
Portland, OR