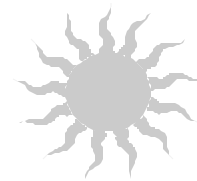


DOPS NOTES



Department of Pharmaceutical Sciences

Spring/Summer 2001

FROM THE CHAIR

June – time to retreat!

It's that time of year and many of us are getting ready to go up to the mountains again for the DOPS retreat. I'm often asked why we go the trouble of organizing a retreat and there are a number of answers to that question. First and foremost it gives our graduate students an opportunity to give poster and platform presentations in what is hopefully a friendlier atmosphere than they would encounter at a national or international meeting. The faculty think this is very important and I think it shows with the extent of faculty involvement in the retreat. Secondly, we have been doing quite a lot of faculty recruiting over the last couple of years and this is an opportunity to get to know the research of our new faculty members in more detail. We have a number of new faculty and research faculty presenting at this year's retreat. One of my favorite reasons to hold a retreat is that there is nothing worse than having to travel to an international meeting to find out what is going on in the lab next to you. I have been at a number of institutions where this was the case and by having a retreat we can hopefully increase the awareness of what is going on throughout the department. This assists students in rotation/lab choices and faculty with respect to potential collaborations. Finally, as faculty we spend a lot of time talking about administrative issues at the retreat we can focus on and celebrate the research that we have ongoing in our department (sorry - that doesn't get the faculty out of a department meeting during the retreat!). Recently, our school of pharmacy was ranked third in the nation for individual research grants awarded from NIH – this is a great achievement and it is a reflection of the quality of the individuals in our school.

One new thing we will be doing at this year's retreat is having a short workshop on "Teaching and research - finding the balance". This will be run by Susan Paulsen and other faculty and is primarily aimed at graduate students and postdoctoral fellows who may have future interests in an academic career where you have major responsibilities in both research and teaching. Another difference is that this year there will be no John Carpenter or Carlos Catalano who are on sabbatical. So, there will be presumably less criticism of "spots on gels" but maybe not – John may have passed the torch on to someone else to ensure that the message of the importance of quantitation gets across.

I look forward to seeing you up in Winter Park and I hope you have a great retreat.

So why were all those people from NIH here last week?

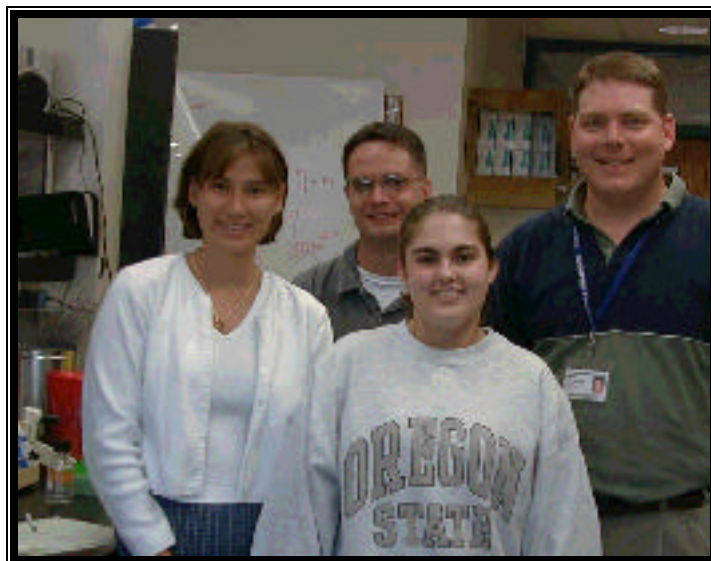
Many of you attended various educational sessions conducted by NIH experts. They were here for a two-day visit which involved fairly detailed meetings with institutional representatives on the first day and faculty outreach sessions on the second day. This wasn't an audit but what is termed a proactive compliance visit. This wasn't a visit triggered by a specific event (yes, that would be bad) and NIH have conducted approximately ten of these procompliance visits at other institutions over the past year. I was involved in the discussions on both days and it was extremely helpful. The site visitors identified lots of positives in our IRB and IACUC, grants management, patent and conflict of interest procedures but also found potential deficiencies. As Dr. Taussig from National Jewish commented, it was like having a large consultancy team visit the university....but this visit was free. I think it's the way to go in the future and enables us to tackle any problems in a non-adversarial environment. So, a very positive visit but expect some changes in our policies down the line.

IN THE SPOTLIGHT The Gustafson Lab

Dr. Daniel Gustafson joined the department in July of 1999, moving from Colorado State University where he was on the faculty in the College of Veterinary Medicine and Biomedical Sciences in the department of Environmental Health. Dr. Gustafson had some help both moving and setting up his lab in the School of Pharmacy as both Mike Long (PRA) and David Carbone (Graduate Student) accompanied him in the move from Ft. Collins. Mike Long has worked with Dr. Gustafson since the summer of 1997, and David Carbone joined the lab at the start of 1999 but has been busy doing rotations, taking classes and TA'ing since beginning the Toxicology graduate program. Andrea Merz is the newest member of the lab, and began working in the Gustafson lab as a PRA on February 1 of this year.

Currently, Dr. Gustafson's research focuses on the pharmacokinetics and pharmacodynamics of cancer chemotherapeutic drugs and drug combinations. Dr. Gustafson's research program is funded by a Howard Temin Award (KO1) from the National Cancer Institute that he was awarded in July of 1998. The Gustafson lab also houses part of the Pharmacology Core for the University of Colorado Cancer Center (UCCC). Dr. Gustafson co-directs this Core with Dr. Mark Duncan. The Core laboratory is responsible for providing analytical and pharmacokinetic modeling support for both clinical and basic science researchers in the UCCC. Mike Long manages the Pharmacology Core laboratory and is responsible for the day-to-day operations. Currently the Pharmacology Core is analyzing patient plasma samples and generating pharmacokinetic data for two ongoing phase I clinical trials and is actively involved in a number of other basic science and clinical studies. Pharmacology Core studies and activities are undertaken in a collaborative manner.

Active research projects in Dr. Gustafson's laboratory include studying the pharmacokinetics of doxorubicin, methotrexate, cyclophosphamide and 5-fluorouracil both alone and in combination. These four cancer chemotherapeutic agents are used in combination in the treatment of breast cancer, but have not been thoroughly studied to determine whether concurrent administration alters the way these drugs act in the body. Ongoing studies incorporate experimentation in animals with computer modeling and biochemical/molecular measurements to measure the likelihood and magnitude of any drug interactions. These approaches allow for the extrapolation of data generated in animals to humans by way of interspecies scaling and computer modeling. Other research projects that are in the planning stage include the development of computer models to study the pharmacokinetics of the taxane drugs (Taxol® and Taxotere®), and studies that look at the role of xanthine dehydrogenase in the metabolism of various drugs. A NIH grant aimed at funding the taxane project is currently under review.



Left to right: Erica Bradshaw, Mike Long, Andrea Merz, and Dr. Gustafson.



FROM DOWN UNDER TO DENVER AND BACK. . .

By Phil Burcham, Ph.D. – (*Dr. Burcham, who worked in Dr. Petersen's lab, recently returned to his home in Australia – philip.burcham@adelaide.edu.au.*)

“Phil, you should think seriously about taking a Sabbatical sometime soon...” Like university faculty everywhere I guess, at Adelaide University (in Adelaide, South Australia) we “endure” annual interviews with our Head of Department where recent progress is reviewed and future goals are set. I had clocked up seven years since my recruitment and my long-suffering boss, Prof. Felix Bochner, thought it was time I took the plunge and experienced the Sabbatical thing first hand. *“Great idea,”* I thought, *“but where?”* Among the hundreds of labs working worldwide on oxidative stress research, choosing one where I would pick up skills and experience directly applicable to my own research endeavors would be challenging.

Thankfully, the task of choosing a destination was facilitated by the fact that, with an American wife who maintains strong affection for “the Mother Country,” only one country was an option! So, I thumbed through my folders of research publications, looking for a US lab to jump out at me. Active interest in protein damage by lipid peroxidation products was my main criterion, but I also wanted a lab headed by a toxicologist with a strong record in aldehyde research. Since papers from Denny Petersen's lab kept cropping up regularly, his group soon moved to the top of my list. So, after a few faxes and emails, I was delighted to find that Denny was happy to host me for the 8 months or so of my study leave. Lots of INS-inspired red tape later, we arrived in Denver in July 2000.

I have always felt that generosity is a defining American character trait, and was delighted to find that Denny is blessed with it in abundance. For him to announce on my first day at DOPS that I was free to work on whatever project I wished - and that he was happy for me to continue our recent work on protein damage by acrolein - was much more than I had hoped for! My group in Adelaide has developed an interest in studying the toxic actions of this

noxious aldehyde at the molecular level, with a view to identifying critical protein targets for acrolein. A postdoc in my Group, Frank Fontaine, had developed a polyclonal antibody that recognizes acrolein-modified proteins with high sensitivity and specificity, at least in *in vitro* model systems and ELISAs. But we were stumped in our efforts to use it in Western blot procedures. None of the usual approaches for optimising Westerns seemed to work. Since we wanted to use this approach to track protein damage during acrolein-mediated toxicity, our lack of progress was pretty frustrating.

So it is very pleasing that months later, after many helpful tips from Denny and others in his lab and around DOPS, I have finally achieved the goals of this work, and am returning to Oz knowing we have a method that reliably detects acrolein-damaged proteins in cells. As often seems to be the case in research, things come together at the end of a project, but, results obtained with the assay are very intriguing, and suggest that acrolein-modified proteins are common even in control cells. This concurs with our suspicion that acrolein could be a rather important contributor to cell damage during oxidative stress.

But it hasn't been all work and no play! We've also had time to visit some of the great attractions of the American West: we've been “wowed” by the Rockies, Colorado National Monument, Yellowstone and Mt. Rushmore. As with most Aussies, we live on the habitable coastal margins of the massive Island Continent. Getting to see big canyons and amazing chunks of rock is something most of us experience only a few times in a lifetime!

I want to thank all who helped make my time in DOPS enjoyable and profitable, including Denny Petersen and his Band of Merry Men: John Piper, John Reichard, Brante Sampey and Steve Luckey. (Mindy doesn't quite fit into that category, but she is a relative newcomer!) Thanks also to friendly folk in the neighboring Ross and Tanguay labs (especially Adil, who gave me someone to discuss Australian cricket results with!). Thanks also to Kirsten for helping with animal supply and maintenance.

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WELCOME

Please join us in welcoming the following new faculty members to the Department:

Dr. Rajesh Agarwal, Professor

Dr. Agarwal received his under graduate and post-graduate education at Lucknow University, India. From 1989-1998, he was Assistant Professor at Case Western Reserve University, Cleveland and prior to joining DOPS, he worked at AMC Cancer Research Center, Denver, as a Senior Scientist.

The major goal of Dr. Rajesh Agarwal's research program is to evaluate the cancer chemopreventive effects of naturally occurring dietary constituents in different animal tumor bioassay systems, and define the mechanisms of the preventive effects at molecular level. Based on the outcome of these studies identifying potentially effective agents in multistage murine skin carcinogenesis protocols, studies are also being conducted to assess the usefulness of these agents for the prevention and/or therapy of other malignancies such as breast and prostate cancers.

Currently, Dr. Agarwal's lab is evaluating the efficacy of milk thistle extract, silymarin, silibinin, phytic acid, grape seed extract, different procyanidins, etc., either alone or in combination with conventional therapeutic agents in prostate, breast and skin cancer models.

Dr. Chapla Agarwal, Asst. Research Professor

Dr. Agarwal received her Ph.D. from Lucknow University in India. She subsequently did her post doc at Case Western Reserve, where she was later promoted to Sr. Research Associate. Dr. Agarwal works in collaboration with Dr. Rajesh Agarwal and also has her own independent research program on Grape Seed Extract and Prostate Cancer.

Dr. David Bain, Assistant Professor

Dr. Bain received his Ph.D. in molecular biophysics from Johns Hopkins University under the training of

Dr. Gary Ackers. His graduate work focused on a thermodynamic analysis of the protein-protein and protein-DNA interactions that regulate the life-cycle of lambda bacteriophage and his post-doctoral work was carried out at the University of Colorado Health Sciences Center in the Department of Medicine. There he studied the structural and biophysical properties of progesterone receptor isoforms and their role in breast cancer. This work laid the groundwork for the more detailed physico-chemical analysis of receptor function to be carried out here at the School of Pharmacy

Dr. Bain's research interests focus on obtaining a quantitative understanding of how gene regulatory assemblies work, and how the physics and chemistry of the transcription complex become the biology of gene regulation. As a model system, he is studying the human progesterone receptor and its role in transcriptional activation. Progesterone receptor is an interesting protein not only because of its complex properties, but also because pharmaceutically important drugs regulate its function. How these ligands function is not at all clear, and elucidating their mechanisms of action will be an important component of his future research.

Dr. Franco Basile, Asst. Research Professor

Dr. Franco Basile received his Ph.D. in Analytical Chemistry from Purdue University in 1992. He completed his postdoc at the Colorado School of Mines, Golden, where he was later promoted to assistant research professor. Dr. Basile works with Prof. Mark W. Duncan and manages the Biochemical Mass Spectrometry Facility. His research interests involve novel approaches to protein separation and quantification with mass spectrometry.

Dr. Lori Kisley, Asst. Research Professor

Dr. Kisley received her Ph.D. from the University of Pennsylvania in 1999. She started her postdoc work with Dr. Malkinson in 2000, with the goal of determining the roles of nitric oxide and the cyclooxygenase (COX) enzymes in lung inflammation and lung cancer. A significant part of her research with Malkinson lab involves

Cont. from page 4

establishing whether anti-inflammatory drugs are effective chemopreventive agents for lung cancer.

And, welcome to new staff, as well. . .

Agarwal Lab

Sivanandhan Dhanalakshmi, Visiting Research Assoc.

Dr. Rana Singh, Visiting Research Associate

Dr. Alpha Tyagi, Visiting Research Associate

Dr. Anil Tyagi, Visiting Research Associate

Bain Lab

Mike Miura, PRA

Gustafson Lab

Andrea Merz, PRA

Malkinson Lab

Brad Barrett, PRA

Petersen Lab

Melinda Taylor, PRA

Charles Salgovic, PRA

John Thompson Lab

Joe Gomez, PRA

Mike Jones, PRA

DOPS Office

Jackie Milowski, Admin. Asst. III

FACULTY NEWS

CONGRATULATIONS

Dr. Susan Paulsen

2001 Chancellor's Excellence in Teaching Award

Dr. Dennis Petersen

2001 Graduate School Mentoring Award

Dr. Tom Anchordoquy

P3 Class - Faculty of the Year

Dr. David Pyatt

D1 Class - Faculty of the Year

Dr. David Thompson

P3 Class - Faculty of the Year

Publications:

Lee, H., Williams, S.K.R., Allison, S.D., and **Anchordoquy, T.J.** Analysis of self-assembled cationic lipid-DNA gene carrier complexes using flow field-flow fractionation and light scattering. *Anal. Chem.* 73(4):837-843 (2001).

Anchordoquy, T.J., Allison, S.D., Molina, M.d.C., Girouard, L.G. and Carson, T.K.. Physical Stabilization of DNA-based Therapeutics. *Drug Discovery Today* 6 (9): 441-448 (2001).

Choosakoonkriang, S., Wiethoff, C.M., **Anchordoquy, T.J.**, Koe, G.S., Smith, J.G., and Middaugh, C.R. Infrared spectroscopic characterization of the interaction of cationic lipids with plasmid DNA. *J. Biol. Chem.* 276 (11):8037-8043 (2001).

Miller, M.S., Gressani, K.M., Leone-Kabler, S., Townsend, A.J., **Malkinson, A.M.**, and O'Sullivan, M.G. Differential Sensitivity to Lung Tumorigenesis following Transplacental Exposure of Mice to Polycyclic Hydrocarbons, Heterocyclic Amines, and Lung Tumor Promoters, *Exp. Lung Res.*, 26:709-730, 2000.

Linnoila, R.I., Szabo, E, DeMayo, F., Witschi, H., Sabourin, C., and **Malkinson, A.M.** The Role of CC10 in Pulmonary Carcinogenesis: From a Marker to Tumor Suppression. *Ann. N.Y. Acad. Sci.* 923: 249-267, 2000.

Cho, C.W., Liu, Y., Yan, X.D., Henthorn, T., and **Ng, K.** Carrier-mediated uptake of rhodamine 123 - implications on its use for MDR research. *Biochem. Biophys. Res. Commun.* 279:124-130, 2000.

Liu, Y., **Ng, K.**, and Lillehei, K. Time course analysis and modulating effects of established brain tumor on active-specific immunotherapy. *Neurosurg. Focus* 9:1-9, 2000.

Ross, D., Winski, S.L., Kepa, J.K. Anwar, A. and Siegel, D. NAD(P)H:quinone oxidoreductase 1 (NQO1). *Chem. Biol. Interact., Special edition on Bioactivation enzymes, ed: Ross, D. and Pritsos, C.A.*, 129, 77-97, 2000.

FACULTY NEWS (cont.)

Winski, S.L., Swann, E. Hargreaves, R.H.J., Butler, J., Moody C.J. and **Ross, D.** Relationship between NQO1 levels in a series of stably transfected cell lines and susceptibility to antitumor quinones, *Biochem. Pharmacol.* 61 1509-1516, 2001.

Siegel, D., Anwar, A., Winski, S.L., Kepa, J.K., Dowd, K.L. and **Ross, D.** Rapid polyubiquitination and proteasomal degradation of a mutant form of NAD(PH):quinone oxidoreductase 1. *Mol. Pharmacol.* 59 263-268 2001.

Moore, J.K., **Schienman, R.L.**, and BellgraU, D. The identification of a novel T cell activation state controlled by a diabetogenic gene. *J. Immunology* 166:241-248, 2001.

Tao, Y., Williams-Skipp, C. and **Scheinman, R.L.**, Mapping of glucocorticoid receptor DNA binding domain surfaces contributing to transrepression of NF- κ B and induction apoptosis. *J. Biol. Chem.* 267 (4) 2329-2332, 2001.

Lectures /Presentations:

Liu, Y., Lillehei, K. and **Ng, K.** Low intensity ultrasound-induced hyperthermia as a new paradigm for shutting down P-glycoprotein, at the 3rd FEBS Advanced Lecture Course ATP-binding Cassette (ABC) Proteins: From Multidrug Resistance to Genetic Disease, March 3-10, 2001, Gosau, Austria.

Liu, Y., Lillehei, K. and **Ng, K.** Overcoming p-glycoprotein mediated efflux by ultrasound-induced hyperthermia. Inaugural Pharmaceutical Congress of America Meeting, Orlando, FL, March 25-29, 2001)

Liu, Y., Cho, C.W., Yan X.D., Henthorn, T., and **Ng, K.** Active uptake of rhodamine 123 by p-glycoprotein expressing cells: implications on the use of rhodamine 123 for multi-drug resistance research.

Inaugural Pharmaceutical Congress of America Meeting, Orlando, FL, March 25-29, 2001.

Liu, Y., Lillehei, K. and **Ng, K.** The use of low intensity ultrasound-induced hyperthermia to increase cellular uptake of lipophilic anti-tumor drugs - a case study of enhanced effects of BCNU against rat glioma. Inaugural Pharmaceutical Congress of America Meeting, Orlando, FL, March 25-29, 2001.

Ross, D. NQO1 (DT-Diaphorase). Chemoprotection, bioactivation and polymorphisms. Invited symposium speaker, Society of Toxicology Annual Meeting, San Francisco, March 29, 2001.

Ross, D. Biochemical basis of NQO1 (DT-diaphorase) polymorphisms. Relevance for chemotherapy and chemoprotection. Invited seminar, Department of Environmental and Occupational Health, Graduate School of Public Health, University of Pittsburgh April 5, 2001.

Ross, D. Biochemical basis of NQO1 (DT-diaphorase) polymorphisms. Relevance for chemotherapy and chemoprotection. Invited seminar, Department of Pharmacology, School of Medicine, University of Pittsburgh April 6th 2001.

Ross, D. Characterization of a mechanism-based inhibitor of NAD(P)H:quinone oxidoreductase 1 (NQO1) using a combined biochemical and proteomics approach, AACR Annual Meeting, New Orleans, March 24-28, 2001.

Grants:

Agarwal, R. The Breast Cancer Fund - Innovative Research Grant. \$50,000.

Carpenter, J. Subcontract U. of Michigan, National Heart, Lung and Blood Institute. \$52,521. 2/1/01-3/31/02

Kisley, L. American Cancer Society Postdoctoral Fellowship. The Role of Cyclooxygenase Enzymes

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and Nitric Oxide in Lung Tumorigenesis. \$118,000. 7/1/01-6/30/04.

Petersen, D., Vasiliou V. NIH/NIAAA. Lipid Aldehydes and Ethanol-Induced Liver Damage. \$1.25 million (direct costs). 06/01/01-3/31/06

Tanguay, R. NIH/NIAAA. "Zebrafish: A model for fetal ethanol injury." \$448,597 (total cost). 06/01/01- 05-31/04.

STUDENT NEWS

(Beginning with this issue, we will be highlighting 1-2 students, in their own words.)

Latoya Jones, Ph.D.

Latoya successfully defended her thesis on February 27 and has since accepted a postdoctoral position with the Univ. of Kansas

Like many in this department, my educational background was not pharmacy. Prior to enrolling in the pharmaceutical science program at UCHSC, my training was in chemical engineering. I obtained a B.S. in chemical engineering from Yale University in 1994. While at Yale, I did an independent study project with Ted Randolph, who later became my M.S. thesis advisor. I came to Colorado in 1994 to begin graduate school in chemical engineering, and in 1996, I obtained an M.S. in chemical engineering from CU-Boulder under the direction of Ted Randolph. I was first introduced to pharmaceutical sciences while I was in the chemical engineering department at CU-Boulder as a result of a collaboration between John Carpenter, who is now my Ph.D. advisor, and Ted. My Ph.D. thesis work has focused in the physical stability of proteins and the effects of pharmaceutically relevant excipients on protein stability. Outside the lab, I've tried my hand (or shall I say feet) at skiing, snowboarding, and hiking. I must say that growing up in Alabama did not prepare me for the technical aspects of gliding on the snow with a plank attached to my feet! In a little over a week from now, I am moving to Lawrence, KS to begin a postdoctoral position in Russ Middaugh's lab in the Pharmaceutical Chemistry

Department at KU. Presently, I envision a focus of my postdoctoral research to relate to characterizing antiviral vaccines. Eventually my plans are to seek a research and teaching position at a university.

Stephen Lucky

I am originally from Cincinnati, Ohio and attended the University of Dayton where I was a chemistry major with a biology minor. I worked with a professor there synthesizing DNA-binding drugs, which first sparked an interest in research in the biomedical sciences. I read about Toxicology on a bulletin board outside of the chemistry office at UD and thought that it captured a broad field of health science and subsequently incorporated my passion for the environment, so I applied to several Toxicology programs across the nation. Luck would have it that I was accepted to Colorado and ended up in Dr. Dennis Petersen's laboratory. My interest lies in exploring the role of Kupffer cells in the progression of chemically-mediated liver injury. I am anticipating a summer defense and moving on to an academic postdoctoral position somewhere in the Toxicology field. My goal for the time being is to attain an academic teaching position and continue independent research in an area that I have not yet determined.

"NOTES" WORTHY

Shari and Robert Tanguay were blessed with a sweet addition to their family -- Lilly -- a beautiful little girl, as is evidenced by the photos on Robert's office door. Look for photo updates on the door from the proud father!

Shannon Winski, Post Doc in the Ross lab, has accepted a position with Gilead in Boulder. In her spare time, Shannon will continue making her beautiful hand-blown glass beads and jewelry, which she will be selling on-line when her website is up and running.

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MARK YOUR
CALENDARS

June 13-15 – DOPS Annual Retreat
Iron Horse Resort, Winter Park

June 21 – Toxicology Seminar
Curtis Harris, MD
*Molecular Carcinogenesis & Molecular
Epidemiology of Human Cancer*

July 11-14 – 2001 MDDC Conference
Breckenridge

September 20-21 – Mountain West SOT
Angel Fire Resort, New Mexico

SPORTS CORNER



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**CAN YOU GUESS
WHO, WHAT, WHEN & WHERE**

DOPS Notes is published on a quarterly basis.
We welcome your comments, articles and contributions.

David Ross, Chair
Carol Carper
Jackie Milowski
Cathy Sandoval

DOPS RETREAT
2001

Winter Park