

Indiana University Cancer Center Newsletter

May 1999

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In the spotlight.....

Jim Drummond, Ph.D.

First, my thanks to the Cancer Center for a brief turn in the spotlight! I'm still pretty new, having settled in at the Bloomington campus a little less than two years ago. Strangely enough, details of my previous lives are rapidly fading. Basically, I'm a synthetic chemist, turned enzymologist, who has found his way into a Biology Department by studying DNA metabolism in cancer cells. Research in my lab is divided between asking mechanistic questions about the human DNA mismatch repair pathway, and understanding how this pathway contributes to either tumorigenesis or drug sensitivity. That's what I want to tell you about in this article.

Imagine, for a moment, a few of the basic transactions in the cell that involve DNA. A substantial effort goes into synthesizing purine and pyrimidine building blocks, followed by their conversion into nucleotides. Replication of the genome using these nucleotides then involves a complex array of proteins that synthesize a second copy of the genome. That's roughly three billion base pairs for a human, an enormous challenge if one assumes that faithful reproduction occurs. Following replication, enzymes called topoisomerases disentangle DNA strands that become intertwined. Ultimately, when the cell is ready for division, the DNA must be condensed, aligned and carefully aliquotted between the two daughter cells. If you imagine all the drugs currently available to treat tumors, you'd probably be very hard pressed to find one that didn't disrupt one of these events.

We focus on the function of the human mismatch repair pathway. The wealth of basic research assembled about the mechanism of mismatch recognition and repair in bacteria and yeast yielded sudden and immense dividends for cancer biologists during this decade. The connection of the two fields resulted in an intuitively satisfying explanation for hereditary cancer syndromes, such as hereditary non-polyposis colorectal cancer and Muir-Torre syndrome, based on loss of DNA mismatch repair. Given a three billion base-pair human genome, and a replication machinery that misincorporates on the order of once in a million bases, roughly three thousand mistakes are predicted with each replication event. The mismatch repair pathway senses these errors and corrects them; loss of such repair opens a Pandora's box of mutational events. If that wasn't bad enough, hotspots for frameshift mutations reside in specific tumor suppressor genes (and I'm suppressing a strong urge to name a few).

The connection between hypermutability and tumor progression should be enough for us to push towards understanding the basic mechanism of this pathway. Even so, there is a second important reason with immediate implications for cancer chemotherapy. The family of proteins that recognizes mismatches and corrects them also recognizes certain types of DNA damage. Such "damage" includes the lesions caused by cisplatin, and by some of the alkylating agents used to treat tumors. In fact, one may select for drug-resistant tumor cells, either in vitro or in vivo, which have lost this DNA repair pathway. Furthermore, processing of DNA damage by the human mismatch repair pathway has since been implicated in drug-induced apoptosis. As yet, the mechanism by which DNA lesions are recognized and processed by the mismatch repair pathway has not been elucidated; we're seeking to define some of those steps.

Taken together with other recent data, we and others are broadening our view of this "repair" pathway. We believe that a better way to view this pathway is to think of it as a general sensor during DNA transactions. During replication, it senses and repairs mismatches. During recombination, it recognizes mispairings in non-homologous recombined sequences and prevents genetic exchange. When DNA is damaged by certain drugs, it can also act as a sensor for these lesions. Normally, DNA damage is detected and repaired prior to replication, but lesions that survive into the synthesis phase of the cell cycle can be acted upon by the mismatch repair proteins. Such processing of DNA lesions appears to serve as one of the triggers for apoptosis in tumor cells. In a medical setting, one might certainly benefit from knowing the status of the mismatch repair activities in tumor cells prior to attempting chemotherapy.

Alas, all is darkening as the spotlight fades! If you'd like to learn more (including gene names) drop me a line jdrummon@bio.indiana.edu.

Sarcoma Program Reorganizes

The Indiana University Cancer Center interdisciplinary sarcoma program is in the process of being re-organized in order to foster increased interactions and research collaboration. While the final details are not yet in place, the re-organized group will be led by Drs. Blythe Thomson (Pediatrics), Bob Timmerman (Radiation Oncology), and Dan Wurtz (Orthopedics). The program will further develop an interdisciplinary clinical program and stimulate research interactions, particularly translational research. Research support to the program is provided in part by the Bone Cancer Research Fund, a philanthropic fund dedicated to research and ultimate cure of osteosarcoma. To this end, the program is funding two translational projects. One is being conducted by Drs. Thomson and Mark Kelley and is entitled "An immunohistological evaluation of the redox and repair activities of apurinic/aprimidinic endonuclease (APE) in pediatric sarcomas with implications for future therapeutic modulation." The second is an ongoing project of Dr. Rose Fife entitled "Effects of doxycycline and a synthetic chemically modified tetracycline (CMT), COL-3, on a model of human osteosarcoma in athymic mice."

A key member of the program is Dr. Dan Wurtz. Dr. Wurtz completed a residency in Orthopaedic Surgery in the U.S. Air Force at Wilford Hall Medical Center in San Antonio and a fellowship in Musculoskeletal Oncology at the University of Chicago. Prior to his arrival at I.U., he held faculty positions at Uniformed Services University of Health Sciences and the University of Oklahoma.

1999 Pilot Project Recipients

To stimulate multi-disciplinary and translation research the Indiana University Cancer Center awards pilot proposals for cancer research to its Cancer Center members. This years recipients

are:

Experimental Therapeutics

- J.T. Zhang, Ph.D.-“Circumvention of MRP-mediated drug resistance in human cancers: A novel peptide therapy approach.”

Osteosarcoma

- Drs. Blythe Thomson and Mark Kelley- “ An immunohistological evaluation of the redox and repair activities of apurinic/apyrimidinic endonuclease (APE) in pediatric sarcomas with implications for future therapeutic modulation.”

Adult Oncology

- Drs. Mark Kelley, Richard Foster, and Liang Cheng- “ Elevated expression of the DNA repair/redox enzyme APE/ref-1 prostate cancer: Diagnostic and therapeutic implications.”

Hematopoiesis

- Mark Kaplan, Ph.D.- “Role of IL-12 in the cytotoxic function of NK and NKT cells.

David Ohannesian, Ph.D. Receives NRSA

David W. Ohannesian Ph.D., a postdoctoral research associate in the laboratory of Dr. Leonard C. Erickson in the Indiana University Cancer Research Institute, has received a National Research Service Award (NRSA) for his project entitled “Isolation of Genetic Suppressor Elements for MGMT” from the National Cancer Institute. The award is for three years. The project will focus on using molecular genetic techniques and gene therapy to sensitize tumor cells to the chloroethylnitrosourea class of chemotherapeutic drugs. Dr. Ohannesian is a member of the Department of Pharmacology and Toxicology.

Seminars/Conferences/Meetings

Monday, May 3

4:00 p.m. “ **Intracellular Signaling Mechanisms Regulating Glucose Uptake and Glycogen Metabolism in Contracting Skeletal Muscle**”. Dr. Laurie Goodyear, Dept. of Medicine, Harvard Medical School and Instructor, Joslin Diabetes Center. **Medical Science 326.**

4:30 p.m. Hematology Fellows Lecture. “**Hepatocellular Carcinoma.**” Fellow. *RT 425.*

Wednesday, May 5

7:00 a.m. Skull Base Group Conference. *UH 2005.*

12:30 p.m. Radiation/Gynecologic Oncology Conference Case Presentation/Didactic. *RT 425.*

4:00 p.m. “**Signal Transduction by Stress-Activated MAP Kinases.**” Roger J. Davis, Ph.D., Howard Hughes Medical Center. *Cancer Research Institute Auditorium 101.*

Thursday, May 6

4:00 p.m. “**Control of Gene Expression During T-Cell Development.**” Gerald Siu, Ph.D., M.D., Dept. of Microbiology, Columbia University College of Physicians and Surgeons. *Medical Science 326.*

Monday, May 10

4:00 p.m. “**InsP3 Receptors and Their Degradation via the Ubiquitin/Proteasome Pathway.**” Dr. Richard Wojcikiewicz, Dept. of Pharmacology, SUNY Health Science Center, NY. *Medical*

Science 326.

4:30 p.m. Hematology Fellows Lecture. **“Antibiotics in Myeosuppressed or Immunosuppressed Cancer Patients.”** Mitch Goldman, M.D., IUSM. *RT 425.*

Wednesday, May 12

12:30 p.m. Radiation/Gynecologic Oncology Conference Case Presentation/Didactic. **“Adjuvant RT for Early Stage Endometrial Cancer.”** Dr. Mark Randall, Radiation Oncology. *RT 425.*

4:00 p.m. **“Novel Signal Transduction Pathways Involved in Transformation by the BCR/ABL Oncogene.”** James Griffin, M.D., Director, Leukemia Program, Dana Farber Cancer Institute. *Cancer Research Institute Auditorium 101.*

Thursday, May 13

4:00 p.m. **“Antiangiogenic Barriers to Tumor Growth.”** Noel P. Bouck, Ph.D., Dept. of Microbiology/Immunology, R.H. Lurie Cancer Center, Northwestern University Medical School. *Medical Science 326.*

Friday, May 14

12:00 noon **“Regulation of the Multidrug Resistance Protein (P-glycoprotein) by Phosphorylation.”** Dr. Guillermo Altenberg, Dept. of Physiology/Biophysics, University of Texas at Galveston. *Medical Science A506.*

Monday, May 17

4:30 p.m. Hematology Fellows Lecture. **NO LECTURE-ASCO.**

Tuesday, May 18

12:00 p.m. Experimental Therapeutics Research Program Meeting. **“TBA.”** *Cancer Research Auditorium 101A.*

Wednesday, May 19

12:30 p.m. Radiation/Gynecologic Oncology Conference Case Presentation/Discussion. *RT 425.*

4:00 p.m. **“Renal Metabolism: Nephrotoxicity and Drug Design.”** Adnan Elfarra, Ph.D., Dept. of Toxicology, University of Wisconsin at Madison. *Cancer Research Institute Auditorium 101.*

Thursday, May 20

4:00 p.m. **“Oral Tolerance: Immune Mechanisms and Characterization of TH3 (TGF-B Secreting) Regulatory Cells.”** Howard L. Weiner, M.D., Harvard Medical School. *Medical Science 326.*

Monday, May 24

4:00 p.m. **“Genetic Analyses of Lymphocyte Development and Function.”** Dr. Jianzhu Chen, Dept. of Biology, Massachusetts Institute of Technology. *Medical Science 326.*

4:30 p.m. Hematology Fellows Lecture. **“Imaging in Oncology.”** Drs. Ken Kopecky and Dewey Conces, IUSM. *RT 425.*

Wednesday, May 26

12:00 noon **“Breast Cancer Screening.”** National Center of Excellence in Women’s Health Seminar. Victoria Champion, Ph.D., Associate Dean, IU School of Nursing. *Cancer Research Institute Auditorium.*

12:30 p.m. Radiation/gynecologic Conference Case Presentation/Didactic. Gregory Sutton, M.D. *RT 425*.

4:00 p.m. **“The Relationship Between Apoptosis and Metastasis”**. Martin Tenniswood, Ph.D., Professor, University of Notre Dame. *Cancer Research Institute Auditorium 101*.

Questions? Suggestions? Announcements?

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