

Indiana University Cancer Center Newsletter

October 1999

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In the spotlight.....

Alexander Dent, Ph.D.

I'd like to thank the academy for this honor, or whoever is in charge of getting people to write about themselves for the Cancer Center.

My Formative Years

I guess I should tell you something about myself. My story begins in a little town in northern California lo some thirty-seven years ago. A spanking baby boy was born to Mr. and Mrs. Dent, and they named their son "Alexander". In a couple of years, my family moved to southern California, and they took me with them. I had a happy childhood growing up in Los Angeles. I did all the wholesome things kids used to do before video games and computers came along, and before the neighborhoods became too dangerous to play in. But that's another story. The important point for the sake of this essay is that in high school, I became quite interested in biochemistry. When I first went to college, however, I was more interested in being a writer or an artist than a scientist. Then, in my second year of college, around 1982, I read a "Newsweek" article about the advances that were being made in gene cloning and genetic engineering. This new field really sparked my interest and I decided to major in biochemistry. I graduated from UCLA in 1985 with a Bachelor of Science degree. At UCLA I had become interested in the problem of biological aging, and I did volunteer work for a doctor who did aging research in mice. I soon found out that aging was a difficult problem to study. However my foray into aging led me into the field of immunology, since aging has profound effects on the immune system. Immunology was something I could get excited about, and it was also a field that was blossoming at that time. I decided to pursue a Ph.D. in immunology at UC San Diego. I was fascinated with the prospect of combining gene cloning and immunology. I joined the lab of Steve Hedrick, who had made a big splash with Mark Davis a few years earlier by cloning the T cell antigen receptor. My thesis in Steve's lab revolved around making transgenic mice for an unusual form of the T

cell antigen receptor called the gamma-delta receptor. Since my thesis dealt with T cell development in the thymus, my thoughts started turning towards how genes were regulated during development and how transcription factors controlled this process. I therefore decided to do a post-doctoral fellowship with Louis Staudt at the National Cancer Institute in Bethesda, Maryland, which was part of the NIH campus. Lou had done his post-doctoral work with David Baltimore, and had cloned the Oct-2 and Oct-3 transcription factors. The Oct factors were the first examples of homeobox proteins in vertebrates.

My NIH Experience

I spent six long years at the NIH, 1992-1998. It was without too much exaggeration, the best of times and it was the worst of times. A lot happened while I was there. The field of molecular biology became an awesome force, and I got swept away in the current. I did learn a lot, I did a ton of science, and I embarked on the job hunt that led me here. On the personal front, I became a father, and matured in many ways (not to say that I am truly "mature" now). Another thing I did at NIH was draw cartoons for the intramural newsletter, "The Catalyst". The cartoons essentially satirized post-doctoral life at the NIH. I achieved more notoriety for drawing these cartoons than I ever imagined, and I am pretty sure that my cartoons were more widely read than any scientific paper I ever wrote. All right, all right. For people who actually care about what science I did as a post-doc, I spent my time cloning and characterizing new transcription factors that were expressed in the immune system. We used a somewhat unimaginative yet effective way of getting new transcription factor genes: to use an automated DNA sequencer to randomly sequence cDNAs that had been enriched for lymphoid specific sequences by subtractive hybridization. I cloned and characterized two new transcription factors: LYSP100 and BCL-6. I eventually moved completely onto BCL-6 when it became clear from other labs' work that BCL-6 was an important oncogene involved in B cell lymphoma. My most fruitful experiment as a post-doc was to make a knockout mouse for BCL-6. That allowed me to find that BCL-6 plays a critical role in lymphocyte differentiation. BCL-6 is required for the formation of germinal centers, which is an important cellular compartment for the maturation of the antibody response to antigen. An unexpected finding was that BCL-6 is also important for the regulation of inflammation, since BCL-6^{-/-} mice develop a pervasive and lethal inflammation of the heart and lungs. I further characterized the inflammation, and found it was mediated by Th2 lymphocytes. I also found that this Th2 inflammation was independent of IL-4 and STAT6 signaling, which is the normal pathway for Th2 differentiation. Thus, BCL-6 appears to regulate Th2 responses by an alternative pathway. My work on BCL-6 was substantial enough to allow me to look for faculty positions, and so I managed to squeak into a position here at IU School of Medicine, in the Department of Microbiology and Immunology.

So Now What Do I Do?

I moved to Indianapolis in the summer of 1998. My wife and I have poured our life savings into a house out in Avon, which is west of here in Hendricks County. My son was almost 2 when we moved, and altogether it was a very trying time, setting up a house and a lab, and getting our little fellow adjusted. My wife has a Ph.D. in chemistry and has extensive research experience. Currently though, she is taking time off from research to take care of our little guy. She hopes to re-enter the work force very soon. Neither my wife nor I have ever lived in the Midwest, and getting used to living in Indiana has been, shall we say, interesting. I am happy to report that we are comfortably settled now. A major point of happiness is that now that I have a house, I have bought myself a piano. Now I spend most of my free time at home working through Beethoven's Sonatas. But I digress. My lab here is focused on working out a lot of the molecular details of BCL-6. There is much that is completely unknown about this critical gene. For instance, the

signals that turn on BCL-6 in B cells so that a germinal center is formed are completely unknown. I can tell you that any obvious combination of receptor and cytokine signaling does not do the trick. The signaling pathway by which BCL-6 regulates Th2 differentiation is similarly unknown. Also, the mechanism by which BCL-6 can act as an oncogene is obscure. Finally, the genes that BCL-6 regulates in any of these processes are essentially unknown. Thus, there is an incredible amount of work to be done if we are to understand this gene any better. The good news is that we have recently made some headway on both the target genes and how BCL-6 regulates Th2 differentiation. We are currently obtaining data that BCL-6 regulates cytokine gene expression in macrophages. Thus, in the absence of BCL-6, abnormal amounts of these cytokines are produced, which may explain how BCL-6 can regulate inflammation and Th2 differentiation. I am very excited about continuing these studies here at IU. I hope in the future I can set up some fruitful collaborations with people who are interested in how BCL-6 regulates the immune response as well as regulates cancer.

Mark Kaplan, Ph.D. Receives RO1

Mark Kaplan, Ph.D., Assistant Professor, Dept. of Microbiology and Immunology, has received an RO1 from NIAID for his project entitled “**Stat Immunobiology**”.

The project focuses on the role of Signal Transducer and Activator of Transcription (Stat)4 in T cell proliferation by regulation of a cyclin dependent kinase inhibitor p27Kip1; mechanisms of gene transactivation by Stat4 using mice transgenic for mutant Stat4 molecules; and analysis of the roles of T helper subsets (controlled by Stat4) in the regulation of hematopoiesis. These studies will elucidate the role of STAT proteins in lymphocyte proliferation which may impact on understanding how STAT proteins may contribute to cellular transformation and how they regulate genes that may be involved in that process.

Chip Montrose, Ph.D. Receives GI Pilot Project Award

Chip Montrose, Ph.D., Professor of Physiology, Dept. of Physiology & Biophysics, is this years recipient of the Gastrointestinal Cancer Pilot Project Award for his project entitled “**Subcellular Fluorescence Spectroscopy During Oncogenesis**”.

In this one year pilot, Dr. Montrose will look at whether the subcellular distribution and spectral properties of endogeneous fluorophores in the human colonic mucosa will change during oncogenesis. By learning about these basic properties of the colonic mucosa, Dr. Montrose hopes to provide a more rational basis for current methods of cancer diagnosis and treatments, as well as provide information that may help optimize such clinical procedures. Work will be performed in collaboration with Dr. Doug Rex, M.D.

Ken Nephew, Ph.D. Receives GOG Award

Ken Nephew, Ph.D., Assistant Professor of Physiology and Biophysics, IU Bloomington, has received a GOG Award for his project entitled “**Developing Profiles of Methylated Genes in Ovarian Cancer**.”

Six percent of women who die from cancer suffer from ovarian cancer. It is the fourth most frequent cause of death in females, and the most lethal of the gynecological cancers.

In any given cell, the genes expressed determine the appearance and behavior of that cell. The abnormal behavior of cancer cells can be due to changes in activity of genes. An increase or decrease in activity of a gene set plays an important role in both development of a cancer cell and cellular progression to a more aggressive cancer. A powerful mechanism for the suppression of

gene activity is DNA methylation. Methylation of key genes is a common event during tumor development. Silencing of genes that inhibit tumor growth, called tumor suppressor genes, by methylation can give a cell a growth advantage, allowing that cell to expand and multiply faster in tumors. The tumor suppressor genes that frequently become methylated are beginning to be identified in colon and breast cancer; however, methylation studies in ovarian cancer are limited, and there is no information on methylation patterns in ovarian cancer. Using a unique screening system that we developed, called differential methylation hybridization (DMH) we can determine the overall methylation pattern and use it like a "fingerprint" to identify different types or stages of ovarian tumors. We believe that by determining the degree of methylation in ovarian tumors, we can identify specific patterns of molecular alteration associated with clinical parameters, providing important information for management decisions in patients. These studies may provide comprehensive profiles of genetic changes for different types of ovarian cancer cells. Translational research is just beginning to search for unique genetic identifiers (i.e., molecular signatures) in clinical specimens. This type of study will pave the way for changing the diagnosis and classification of ovarian tumors from the current histopathological approach into the more precise molecular basis.

Cancer Biology Training Awards

The Cancer Biology Training Program came into being in response to a request from William Bosron, Assistant Dean for Graduate Studies, for training programs for which seed money might be obtained through the IUPUI Fellowship Committee. Dr. Ann Roman, Professor of Microbiology & Immunology, responded to this request by designing a program based on the expertise of individuals within the IUCC. Dr. Bosron's application was successful and the IUPUI Fellowship Committee gave a Fellowship Block Grant to the School of Medicine Graduate Division to provide stipends for this new interdisciplinary program. These funds were, in turn, passed on to Dr. Roman to administer. The purpose of the funds is to establish a documented record of success and show institutional support for training in this area. The training program itself is currently being developed. The eventual goal is to be competitive for an NIH T32 training grant. Three partial stipends were awarded for this academic year to current predoctoral students working in the area of cancer biology. This years recipients are:

- Stacy Nelson from the Department of Microbiology and Immunology
- Melissa Limp-Foster from the Department of Biochemistry & Molecular Biology
- Dean Wiseman from the Department of Biology.

New Faces

Ahmad Safa, Ph.D., joins the faculty as of October 1, 1999, as a member of the Dept. of Pharmacology & Toxicology. Dr. Safa received his Masters Degree and Ph.D. in Molecular/Cellular and Developmental Biology from Iowa State University. He was a research associate at the University of Louisville, and a visiting fellow at the National Cancer Institute. He then took a faculty position at the University of Chicago as Assistant Professor of Medicine. He comes to us from the Medical University of South Carolina where he was Professor of Experimental Oncology. His research interests center around multi-drug resistance in human tumors where he is nationally recognized for his work. Dr. Safa's laboratory and office are located in the Cancer Research Institute Room 132 and Room 119. You can reach Dr. Safa at 8-4952.

Robert Nelson, M.D., is an Associate Professor of Medicine in the Division of

Hematology/Oncology and Bone Marrow Transplantation Service. He graduated from Indiana University and Indiana University School of Medicine. He was an Allergy and Immunology Fellow at the University of Southern Florida College of Medicine and Affiliated Hospitals and a Bone Marrow Transplantation Program Visiting Fellow at the Medical College of Wisconsin. His research interests are in clinical research in allogeneic hematopoietic stem cell transplantation; immunodeficiency diseases in adults and children; and hematopoietic stem cell transplantation for autoimmune diseases. Dr. Nelson's office is located in the Cancer Pavilion Room 439 and he can be reached at 4-0920.

Seminars/Conferences/Meetings Located on the Web Page

Due to the ever increasing number of monthly seminars/conferences/meetings, you can now find these schedules on the Indiana University Cancer Center web page under Seminars and Conferences.

IU Cancer Center Web Page Address

www.iupui.edu/~iucc/

If you have a conference or meeting that is not posted and you would like it posted please contact:

Elizabeth Parsons (eparsons@iupui.edu)

phone 8-0070 or fax 8-0074 and she will have it added to the web page schedule

Questions? Suggestions? Announcements?

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