

Indiana University Cancer Center Newsletter

*A National Cancer Institute-
Designated Cancer Center*

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Special points of interest:

- *In the Spotlight*-Maureen Harrington, Ph.D.
- Cancer Center Names Two Senior Leaders
- Cancer Center Network/Systems Team Expands
- Seminars/ Meetings/ Conference

In the spotlight.....

Maureen Harrington, Ph.D.

A little personal history

I went to Purdue for my undergraduate work – having decided that Dietetics and Nutrition was where my future lay. Yes, this does mean my BS degree is in Home Economics. I followed this with two years at the University of Texas School of Public Health, where I learned that I did not want to spend my life developing nutritional guidelines. The good news was that I did learn that I liked doing bench research (my MS thesis was on mosquito genetics) and that pharmacology might be interesting. So I headed to the University of North Carolina at Chapel Hill for a PhD in Pharmacology.

While learning why and how drugs work was interesting, it wasn't quite what I had in mind. Fortunately UNC was in the process of establishing the Lineberger Comprehensive Cancer Center. As a recent recruit to the cancer center Jack Pledger had joined the Pharmacology Dept and was studying how platelet-derived growth factor controlled the movement of cells through the cell cycle. This was an incredibly exciting time in the cell proliferation field as the concept of cellular proto-oncogenes was developing and *v-sis* turned out to encode the B chain of PDGF. I became involved in a wide variety of projects in the Pledger lab including the regulation of PDGF receptor phosphorylation and PDGF induced protein glycosylation and cytoskeletal rearrangements. While working in the Pledger lab I realized that I next wanted to work on the relationship between cellular proliferation and differentiation. My goal would be to

identify a model system for determining where in the cell cycle and how a cell makes the decision to exit a proliferative cycle and terminally differentiate. At the same time the Pledger lab was in the process of moving. First to Vanderbilt and then to University of South Florida, where Jack is Director of Basic Research at the USF – H. Lee Moffitt Comprehensive Cancer Center.

With my husband David (whom I met in graduate school), I struck out for the University of Southern California to the laboratory of Peter Jones, Director of the USC - Comprehensive Cancer Center. Peter had discovered that a transient treatment of fibroblasts with the DNA demethylating agent, 5-azacytidine resulted in the formation of cells determined to the myogenic lineage that would eventually fuse and form multinucleated myoblasts. I figured this would be a good model system to study how serum derived growth factors would regulate the switch between proliferation and differentiation. So did Peter until a collaborator, Michael Karin, mentioned that techniques were evolving that made it possible to look directly at the binding of transcription factors to DNA. Peter remembered that I needed to learn some molecular biology – and I couldn't turn down the project – since I was able to still keep doing some muscle cell biology at the same time. The Jones' research philosophy also included "it's never too early to start writing grants." Lucky for me the NIH agreed and I received an NIH Post-Doctoral fellowship. Two years into our stay in Los Angeles, my husband, David, was recruited by Boehringer Mannheim and it was back to Indiana.

Research at Indiana University

In a visit to Indianapolis I discussed my quest for individuals studying growth factor action with Howard Edenberg and he said I needed to talk to Hal Broxmeyer. I explained my background and research interests and Hal said I could join his lab as long as I worked on something relevant to hematopoiesis. This I had to think over. If there is one thing a person who works on real growth factors like PDGF knows is that there are a few too many hematopoietic growth factors and besides the cells hematopoietic people work with are transformed. At this point NIH felt compelled to intervene and pointed out that to transfer my NIH post-doc fellowship I needed to extend my training in the area of transcription factors and maybe I should try cloning a promoter. So putting hematopoiesis, transcription factors and cloning together lead to the cloning of the mouse colony-stimulating factor-1 (CSF-1) promoter which was accomplished with the help of Howard Edenberg, and Lucy Carr (then a post-doc in Edenberg's lab).

With the comment that "I think your research is ready for funding; here are the forms for the Leukemia Society, NIH, ACS and" from Hal and an offer of a tenure track position in the Hematology/Oncology Division in the Dept.

of Medicine, I had my chance. Fortunately the Leukemia Society and the NIH found my research fundable. I received a Special Fellow award from the Leukemia Society and an R29 grant from the NIH. Fred Falkenburg then arrived in Hal's lab for a sabbatical. But a week later a paper was published describing the study he had planned – thus he was in search of a new project. Fred, who had an interest in interleukin-1 (IL-1) signaling, thought the control of CSF-1 gene expression sounded entertaining and said he would take pleasure in driving me nuts. Naturally I had earlier explained to Fred that hematopoietic growth factor people don't really understand how to work with growth factors. The collaboration with Fred was wonderful. We differed in our approaches and the combination turned out to be the answer. We were able to publish several papers describing how CSF-1 gene expression is regulated by serum derived growth factors, IL-1 and cellular differentiation. While the CSF-1 promoter-DNA binding protein research also made headway, our progress was frustrated by an inability to regulate the CSF-1 promoter constructs with IL-1 (not that Rob Hromas didn't keep asking). At this point my R29 was up for renewal, so I decided that we needed to understand more clearly the IL-1 signaling pathway. Fortunately the Leukemia Society and the NIH agreed and I received a Scholar Award from the Leukemia Society and my first R01 from the NIH to pursue these studies. During this time Mark Goebel, a Biochemistry Dept/Walther colleague pointed out that the *Drosophila* Toll receptor was similar to the IL-1 receptor. Moreover, downstream components of the Toll pathway, Dorsal and cactus, were similar to members of the c-rel family of cellular proto-oncogenes. Rel family members, like NF-kB are potent transcription factors required for embryonic development and for proper immune system function. Mark thought maybe we should try a genetic approach. So a post-doctoral fellow, Marina Trofimova, set about cloning mammalian counterparts of the *Drosophila* Toll signaling pathway. Without a doubt we have found ourselves in one of the most fascinating research areas ever (not that I am biased).

The first gene Marina cloned was a mouse version of the *Drosophila* pelle serine/threonine kinase, that we call the mouse pelle-like kinase (mPLK). Using a biochemical approach competitors cloned a human version of mPLK, which based upon their cloning strategy, was named IL-1 receptor associated kinase (IRAK). To our surprise (and the amazement of several reviewers), a post-doctoral fellow, Eva Vig, and a graduate student, Melissa Green, determined that tumor necrosis factor (TNF) induced NF-kB activity is mediated in part by mPLK/IRAK, whereas IL-1 induced NF-kB activity is independent of mPLK/IRAK activity. NIH was also amazed with the link between mPLK and TNF induced NF-kB activity and they gave us five years to figure how mPLK mediates TNF dependent activation of NF-kB activity. While a function for mPLK/IRAK activity in the IL-1 signaling

pathway has not been identified, Eva is examining whether mPLK/IRAK is involved in cross-talk between the TNF and IL-1 signaling pathways. Somewhere in this period my daughter Colleen, was born.

We are also characterizing receptor interacting protein 3 (RIP3), a novel serine/threonine kinase that was isolated in our mPLK screen. A post-doctoral fellow in the lab, Nan Pazdernik, has determined that RIP3 contains a novel cell death (apoptosis) inducing domain and can also induce NF- κ B activity. Currently Nan faces the challenge of determining the mechanism through which RIP3 modulates apoptosis, and in which signaling pathway RIP3 belongs. Intriguingly, RIP3 is expressed in developing thymus and intestinal tract epithelium, tissues critical for host defense.

In keeping with our success using genetic approaches, Kang Yu a new post-doctoral fellow has taken two approaches toward understanding how mPLK activity is regulated by TNF and what cellular events mPLK regulates. Based upon reports in the *Drosophila* literature, Kang has cloned out a novel protein, mouse pellino (mPLN) that binds mPLK and is capable of inducing NF- κ B activity. Kang is currently faced with determining whether mPLN activity is dependent upon mPLK and if mPLN modulates mPLK, IL-1 or TNF induced NF- κ B activity. A second approach Kang is taking is to use the yeast two-hybrid system to identify proteins that complex with a new protein, we have named SIMPL, that complexes mPLK to downstream kinases in cells.

Jun Tian, a research associate in the lab is exploring a possible link between mutations in the mPLK/IRAK gene and dyskeratosis congenita, a disease characterized by opportunistic infections, in which patients eventually develop leukemia and die of bone marrow failure. While this is a rare disease, Jun has characterized cells derived from one DKC family, and the affected child had little if any mPLK/IRAK protein, whereas the mother had a normal level. We are quite excited about these studies and hopeful that we will find more DKC families to characterize. While this disease is rare, it is amenable to gene therapy.

The newest member of our group is Sue Brutkiewicz, a senior post-doctoral fellow who is working on a collaborative project between the Harrington, Goebel, Srivastava and Hurteau laboratories. This project centers on using adeno-associated viral vectors, to deliver mutated versions of genes which either block cell cycle progression or induce apoptosis, to epithelial ovarian cancer cells, both *in vitro* and in an animal model. Sue is an ideal person to direct this project as she has a strong background in molecular immunology. With any amount of luck we hope to use this system to study ovarian cancer tumor biology as well.

Cancer Center Names Two Senior Leaders

Victoria Champion, DNS, has been named as the Associate Director of Cancer Prevention and Control. Her duties include the formation of research programs and integrating its members with basic and clinical researchers. Vickie is the Mary Margaret Walther Professor for Cancer Care Research in the School of Nursing.

Larry D. Cripe, M.D., has been named Associate Director of Clinical Affairs. Dr. Cripe's responsibilities include interacting with current programs that support the mission of the Cancer Center to improve access to clinical trails. He has replaced Mike Gordon as the Director of the Adult Clinical Research Office.

Cancer Center Network/Systems Team Expands

Bob Berbeco has joined the Cancer Center as its Network and Systems Manager. His responsibilities include troubleshooting and improving upon the current computer hardware and software systems utilized at the Cancer Center. In addition, Jason Nichols and Brad Brunner have been hired as Computer Support Specialists (part-time), and they are responsible for resolving Help Requests. Please help us welcome them as they join Nicoletta Cornea and Jason Sisk. For computer or network management services, please use the electronic help request form at the following URL.
<http://medicine.iupui.edu/helpdesk/request.asp>

Seminars/Conferences/Meetings

Remember a listing of seminars/conferences/meetings can be found on the Indiana University Cancer Center web page under Seminars and Conferences.

Web Page Address

www.iupui.edu/~iucc/

If you have a conference, seminar or meeting that you would like 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

HAPPY NEW YEAR!