

# Indiana University Cancer Center Newsletter

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## *Special points of interest:*

- *In the Spotlight*-David Seitz, Ph.D., M.D.
- Hari Nakshtratri, Ph.D. receives AICR Grant
- Dwayne Kniola elected President Elect of IOSW
- Cancer Biology Opportunities
- Emiko Kreklau, Ph.D. Receives NRSA from NCI
- Seminars/ Meetings/ Conference

## *In the spotlight.....*

### David Seitz, Ph.D., M.D.

My journey to Indiana and the IU Med Center was meant to last just a year. Sixteen years ago, in exchange for paying a few bills, a little cooking and cleaning, and perhaps a spin now and then with the lawnmower, I took a room in a little bungalow in Broad Ripple. My housemate and I had first met as postdoctoral fellows in chemistry, became fast friends, climbed, skied, and mountaineered in the High Sierra back country, and, in general, fashioned ourselves a bit faster and smarter than the average Hoosier. I could affect such an attitude then; after all, I was only going to be here for a year. And so, in June of 1984, a bit older than the rest of my fellow medicine interns and a little homesick, I began counting down the days. Home then was in Boston, and I had already spent two years as a medical student in Miami.

What could possibly provoke a move from Boston in the first place? The Boston area universities of the late '70's were still in that heady flush of the post student revolution—in look, if not in attitude—and there remained a lingering insouciance for most matters of social decorum. My group of chemistry graduate students exemplified the times—long hair, plenty of it in all the places it could be grown, clothes that only occasionally benefited from a late night visit to the laundromat, but otherwise endowed with sharp minds and a quick wit. “So what’s a (xxxx) narc doing here?” one asked after my entirely unexpected visitor left my office. “He’s a croaker (our slang for MD’s),” I replied. Uncomprehending silence.

I recall stifling a chuckle as Glenn, standing rigidly upright and looking virtually sterile in a dark suit, starched white shirt and tie, polished leather shoes and closely cropped hair, consulted the notes clutched in his hand and painstakingly drew the structure of tamoxifen on my chalkboard. Pausing to brush some dust off his jacket, he turned and told me about his project. I would learn that he was the chief resident in radiation therapy at the Joint Center at Harvard, that as part of a research project, he wanted to radioiodinate tamoxifen, and if he could accomplish that, he then wanted to see if his compound could be used to either image breast cancer, or with a different isotope, perhaps be used to deliver lethal radiation to the tumor. “So, where do you want to stick the iodine?” I asked. After a short pause, and a studied glance at his structure, he continued, “Well, I guess it doesn’t really matter.” “How about *ortho* to that ethoxy group?” I thought out loud. With some hesitation, he pointed his finger toward the middle of the structure, and said, “Here?” I rose from my chair, reached past him, and pointing further toward the right, said, “No, no, that’s a double bond!...(xxxx), didn’t you guys have to pass organic to get into med school?” Of course, only a true romantic would dare point to the long, silent pause that followed, to the swirling confluence

of embarrassment, incredulity, amazement, incomprehension, to that sense that we were each out of place and couldn't we just somehow rewind the tape and record over it with something else, to that all too familiar feeling of why me, why now and why here...yes, only a true romantic would say, some twenty-plus years later that his life was forever changed in that moment.

"Tin, yeah, tin...perfect," I rambled, my finger still pointing toward the *ortho* position. "No, iodine, not tin, its gotta be iodine," Glenn replied with barely concealed anxiety. Now able to laugh, I began in earnest to explain the magic of tin bonded to carbon, how a strong base could abstract just the right proton on tamoxifen, how iodine could nearly instantaneously replace tin, all the while filling the board with structures and arrows and reagents. And over the next several months, Glenn gradually became one of the group. True, he didn't grow his hair out, and kept his Brooks Brothers look, but we learned about breast cancer biology while he learned about tin and carbon, and one fine day, he held a vial of iodotamoxifen in his hand, a huge smile breaking across his face. As was our custom at the time, we voted his accomplishment the winner of the weekly beer award, and on Friday evening, as I did most weeks, I walked across Huntington Avenue, bought beer and we sat outside our labs in the hallway toasting a wonderful synthesis. As the evening stretched into night, Glenn let what little hair he had down, and my graduate students grudgingly admitted that even croakers could do science. And Glenn, surveying the group, replied that he could probably take them out and dress them, but still doubted that any of them could become a physician.

We didn't call this translational research in those days, but nonetheless, my group began hanging out in the radiosynthesis laboratory in the basement of Children's hospital and looked at images obtained when mice implanted with breast cancer were injected with radioiodinated tamoxifen. Several of them extended the chemistry and found that these destannylation reactions could be used to specifically introduce other labels, such as tritium onto biologically active molecules. One spent time learning how to measure the binding affinity of iodotamoxifen for the estrogen receptor. All of us, chemists and biologists, scientists and physicians, were disappointed that iodotamoxifen had virtually no affinity for the estrogen receptor. A few years later, we employed molecular mechanics and semi-empirical techniques to calculate the minimum energy conformations for tamoxifen and a number of its derivatives. Our results showed that substitution at the *ortho* position did not result in appreciable changes in the shape of the molecule, thus confirming that other physical-chemical properties influenced receptor binding. Thinking about the problem today, each of us would likely admit that it was biologically naïve to expect that the introduction of an atom as large as iodine onto a molecule as small as tamoxifen would not perturb affinity for the receptor. For me, though, it was the beginning of a journey that led first to Miami and then to Indianapolis (for a year) on my way back to Boston.

As I begin my seventeenth year in Indianapolis, I have completed the circle and returned to the university. Even though it's now called translational research, I continue to try to refine how scientific questions are informed by clinical problems in oncology. Though my former chemistry students would probably never fess up to this, I think that croakers and scientists can both be bright, and I very much enjoy working with each. Life changes slowly. I still live in Broad Ripple, now with my wife, who was a year ahead of me when I first met her very early one morning in the Wishard ER. I still pay a few bills, do a little cooking and cleaning, and now and then take a spin with the lawnmower. I no longer climb mountains. I have become, quite happily, an average Hoosier.

### **Hari Nakshatri, Ph. D. Receives AICR Grant**

Harikrishna Nakshatri, Ph.D., Assistant Professor, Dept. of Surgery, has received a two year grant from the American Institute for Cancer Research (AICR) for his proposal entitled **"Feverfew, an herbal NF-kappaB inhibitor, in the treatment of breast cancer"**.

Dr. Nakshatri proposes that diets supplemented with herb with anit-NF-kB activity may prevent breast cancer metastasis and increase the response to conventional chemotherapy. It is critical to further confirm the results of cell culture studies in an animal model before clinical studies. In this proposal, using a nude mice breast cancer model (which closely recapitulates human breast cancers), he will examine whether diets supplemented with the active ingredient of feverfew will prevent breast cancer growth, metastasis, and increase the response to taxol treatment.

## Dwayne Kniola Elected President Elect of IOSW

Dwayne Kniola, MSW, LSW, Indiana University Cancer Center social worker, has been elected President-Elect of Indiana Oncology Social Work, Inc. (IOSW) for 2000. He will hold office of President in 2001. Dwayne was also recently appointed as the Indiana State Representation for the Association of Oncology Social Workers (AOSW).

## Cancer Biology Opportunities

### POTENTIAL FUNDING FOR GRADUATE STUDENTS

The Cancer Biology Training Program (CBTP) has again received funds for two predoctoral fellowships. These funds come from the IUPUI Fellowship Committee through an award of a Fellowship Block Grant to the School of Medicine. The purpose of these funds is to allow us to establish a documented record of success and show institutional support for training in this area. This will help us be competitive for an NIH T32 training grant in the future.

We need to identify potential recipients of these stipends for this coming academic year. Potential mentors in the CBTP must be members of the Indiana University Cancer Center and the Indiana University Graduate Faculty. If you wish to have your student(s), who must be a US national or permanent resident, considered for this stipend, I need to receive the following from you: 1) by June 15, the name(s) of the student(s) you would like considered; 2) by June 30, a letter of recommendation including his/her record of publications and presentations, whether or not the student has completed a minor, and the student's status with respect to advancement to candidacy; 3) by June 30, a letter from the student addressing his/her commitment to cancer research. Please send this information to Ann Roman, Department of Microbiology and Immunology, Indiana University School of Medicine. A group of faculty representative of the Departments involved will rank the applicants and identify the recipients. If you have questions, please contact Ann Roman at [aroman@iupui.edu](mailto:aroman@iupui.edu).

### CANCER BIOLOGY MINOR

A new Cancer Biology Minor has been approved by the Indiana University Graduate Council. The description of the minor is the following: A minimum of 12 credit hours outside of the student's major department, including two courses from the following list of four: Q622 Cytogenetics of Malignancies, F819 Chemical Carcinogenesis, J842 Neoplastic Determinants, BIOL516 Molecular Biology of Cancer. At least one credit of G504 Introduction to Research Ethics must also be taken. The remainder of the minor will be selected from the following courses: Graduate G865, G817, G807; Biochemistry and Molecular Biology B807, B810; Medical and Molecular Genetics Q620, Q622; Microbiology and Immunology J805, J807, J828, J829, J837, J840, H842, J854; Pharmacology and Toxicology F819, F820. The minor program must be approved by the student's Advisory Committee which will take into consideration the student's total didactic experience. In the case of combined MD/PhD students, the Committee may approve substitution of appropriate medical school courses. The minor representative on this Committee will be selected from outside the student's major department and must be a member of the Cancer Biology Training Program.

### Emiko Kreklau, Ph. D. Receives NSRA from NCI

Emiko Kreklau, Ph. D., a postdoctoral fellow in Dr. Leonard Erickson's laboratory, has been awarded a National Research Service Award (NRSA) fellowship grant for three years from the NCI to support her research into enhancing chloroethylnitrosourea (CENU) anticancer therapy. The grant is an extension of the Cancer Center Program Project Grant co-directed by Drs. David Williams and Erickson. The primary mechanism of CENU resistance in tumors is the DNA repair protein, MGMT. Phase I gene therapy trials have been ongoing at I. U. to express MGMT in bone marrow progenitor cells by retroviral transduction to improve the therapeutic index of CENU chemotherapy. Prolonged exposure to the free base O<sup>6</sup>-benzylguanine has been demonstrated to inactivate MGMT in tumors *in vitro* and *in vivo* by several groups (Kreklau *et. al.*, J. Pharmacol. Exp. Ther. 291:1269, 1999), and this agent recently underwent Phase I trials as a potential CENU chemomodulator. In collaboration with Dr. Suzanne Ragg, Dr. Kreklau has been studying a MGMT point mutant that exhibits about 1000-fold resistance to inhibition by this agent. The goal of the fellowship is to employ

retroviral transduction to express this mutant in human bone marrow cells transplanted into NOD/SCID mice, and to thereby further intensify CENU therapy in combination with O<sup>6</sup>-benzylguanine.

### **Seminars/Conferences/Meetings**

Schedules are available via the IUCC web page under seminars and conferences.

Web Page Address

**[www.iupui.edu/~iucc/](http://www.iupui.edu/~iucc/)**

If you have a conference, seminar or meeting that you would like posted please contact:  
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