

# Indiana University Cancer Center Newsletter

**April 2000**

## *Special points of interest:*

- *In the Spotlight*-Thomas Gardner, M.D.
- Funding Opportunities
- Mark Kelley, Ph.D., & David Moore, M.D. receive DOD Grant
- Ovarian Cancer Research Committee
- Michael Darling Elected President of ACE
- Seminars/ Meetings/ Conference

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

### **Thomas Gardner, M.D.**

Over the past eight months I have had the pleasure of meeting many of the members of the Indiana University Scientific Community and the NCI Designated Cancer Center. I would like to congratulate all of the contributors in the substantial effort required to obtain a NCI Designation and to thank the Cancer Center Newsletter for the opportunity to introduce myself to the rest of you.

#### **My Formative Years**

I was born in Florida on Homestead Airforce base, which has since been destroyed by a hurricane named Andrew. My family moved up to Long Island, where my dad practiced dentistry and I was just a kid fascinated by my dad's ability to help people. It was around the third grade that I realized that a career in medicine might be both exciting and potentially rewarding. Who would have figured that managed care could spoil such a good thing? I still recall informing my grade school teachers that "I didn't need good penmanship because I was going to be a doctor." Even with my established poor penmanship I was able to graduate High school and head off to college. Enjoying my formative years in the shadow of the Big Apple (that is New York City for you Hoosiers), I took an academic Scholarship at George Washington University to spare my parents the full cost of a college education. This action would be greatly overshadowed by my later decision to stay at GWU and attend the most expensive medical school in the country.

While at GWU, I was able to train and complete the Marine Corps Marathon in three hours and twenty-one minutes. Always striving to be a little different, I received a BA in Computer Science and Information Systems in 1986. The first two years of medical school were full of memorization and books. Running around the reflecting pool and the monuments was always an awesome experience and a good release from the mental rigors of medical school. I still remember meeting a fellow health professional student during one of these runs, her name was Jill and five years later we would be married. After two years of medical school, it was off to the clinic to learn how to practice the art of medicine. My first clinical rotation was primary care followed by a two-week elective in urology and after a short two weeks I was hooked! The combination of surgical and medical management of urologic diseases and the breadth of disorders and wide age range of patients excited and

intrigued me.

### **My Urology Training**

In 1990, after surveying a number of programs throughout the country, I returned to the Big Apple and the New York Hospital-Cornell Medical Center program for a six-year residency. I was pleased last month to see my fellow intern in surgery still as a Cardiac Surgery Fellow on the David Letterman Show (Bobby as Dave called him). This was pleasing because I recall my years of training at New York Hospital very fondly and that he has been training for a decade after medical school and still doesn't have a job and I got one after only nine years. It was during a research rotation that the research bug took a bite out of me and I knew my training would not end with my residency. The daily frustrations of caring for patients with cancer led me to the realization that urology had many limitations in helping patients with urologic malignancies. During my chief residency, I applied for and received an American Foundation of Urologic Disease Scholarship to study prostate cancer cell biology with Leland W. K. Chung at the University of Virginia.

### **My Research Years at the University of Virginia**

It was a two-year fellowship, but it only took about a month for Dr. Chung to kindle that small flame that was lit during my 6-month research rotation into roaring blaze with exposure to the wonders of cell biology, molecular biology and gene therapy. I joined the lab of Dr. Leland W. K. Chung as his first Urologic Oncology Fellow in the institution designed and created by Thomas Jefferson. Dr. Chung had previously had many other fellows while at the MD Anderson Cancer center in Houston, Texas who now hold academic positions throughout the world. I arrived at UVA about six months after Dr. Chung and by that time his lab had about 20 individuals hard at work. Dr. Chung had spent almost 20 years studying and delineating the cellular interactions of prostate cancer epithelial cells with their neighboring and supportive stromal cells. He gave me the mission to try and formally confirm this vital intercellular communication by trying to kill off the "supportive" stromal cells of a metastasis and have the entire tumor be eliminated. I was immediately guided down a trail that would both enlighten me in the wonders of medical research and answer the question that was initially posed when I first met Dr. Chung. With the assistance of Chinghai Kao, senior scientist in Dr. Chung's lab, I was able to construct a retrovirus that would stably confer the herpes simplex virus thymidine kinase (hsv-TK) gene expression to a bone stromal cell that originated in Dr. Gary Balian's Orthopedic research lab at UVA. Using these bone cells (which retained an ability to home to the bone marrow) and some human prostate cancer cells (capable of mimicking the progression we see in men with prostate cancer), I generated an interesting model. This model afforded me the opportunity to establish an osseous prostate cancer lesion in the subcutaneous tissue of nude mice. The model led to the experiments that could answer the stromal-epithelial interaction question initially posed to me by Dr. Chung. I mixed the Bone cells containing the hsv-TK gene and the human Prostate cancer cells. In the simplest of experimental designs, I had four groups 1) prostate cells 2) bone cells, 3) Bone (TK) and Prostate cancer cells and 4) #3 with Acyclovir activation of the TK. This experiment showed that the first two groups grew similarly in size. The combination group grew to greater than the sum of both groups #1 and #2, suggesting synergism. Group four, in which the ACV was administered to kill off all the bone cells was half the size to either Group #1 or #2. The persistence of the subcutaneous mass worried us initially and continues to raise concerns in reviewers of this work, but on histological examination the residual mass appears to be the residual blastic component of the osteoblastic lesion and devoid of prostate cancer cells.

### **Translation this discovery to the Clinic**

As a scientist-physician, my scientific side was pleased with these experimental findings, but as a physician I could not figure out how to translate this finding to help men suffering from metastatic prostate cancer. During the period of my fellowship, Dr Kao and I worked closely together and with assistance of several other post-doctoral fellows was able to generate the pre-clinical data necessary to bring an adenovirus based on this principle to a Phase I trial. This adenovirus was designed to express the hsv-TK gene in the bone stromal cells of an osseous metastasis by using the osteocalcin promoter as a transcriptional regulator. I was pleased during our pre-clinical testing to find out that the prostate cancer cells also could activate this promoter as well. Therefore, we generated a recombinant adenovirus ("common cold virus") to transcriptionally target both components of an osseous metastasis simultaneously. Now this was something that could work in the clinic. Dr. Chung then suggested that submitting an Investigational New Drug Application for a Phase I trial of using this adenovirus (Ad-OC-TK) to treat the terminal form of prostate cancer would polish my urologic oncology training. I was appointed an Assistant Professor of Urology and with the help of my colleagues and support of my wife and family and after receiving UVA's IRB, CCPRC, IBC approvals, I submitted approximately a 692-page application to the FDA on 12/28/98. A mere 340 pages in four subsequent amendments to the FDA application and I was approved as the principle investigator of IND #7335 on March 27, 1999. It was in this same period that I secured an appointment at Indiana University with Dr. Koch and the Department of Urology. Dr. Koch was able to promise me the support and protection that I was told it would take to continue as a Scientist-Physician. Dr. Koch's successful recruitment of Dr. Kao from the University of Virginia will allow Dr. Kao and I to continue our work without inter-institutional hurdles. Six months later after enrolling and injecting the metastases of 12 men with escalating doses of the Ad-OC-TK virus and seeing the safety of this approach in the face of other adenoviral trials facing difficulties suggests that our transcriptional regulation with a tumor-specific promoter was a good idea. Just last week the FDA approved an IND for a Phase II trial of this virus. I am very encouraged with this approach and continue to work in my laboratory to enhance the targeted killing ability of this virus by further modulations of the promoter, the toxin delivered and the delivery approach utilized. I would also like to thank my mom, dad, wife, and kids for their support and the many academic urologists and scientists that I have had the privilege to be inspired by during my training. During the transition and since my arrival I have secured extramural funding thanks to the help of many individuals at IU (Dept of Urology, Dean's office, IBC, LARC, R & S Programs) who assisted me in these efforts.

## **Funding Opportunities**

### ***Research Scholar Grants for Psychosocial and Behavioral Research*** - American Cancer Society.

Grants are \$500,000 for five years with option for renewal. Open to investigators at any stage of their careers. Application deadlines: April 1 and October 15, 2000. Information: <http://www.cancer.org> or [grants@cancer.org](mailto:grants@cancer.org).

***Prostate Cancer Research Program*** - Department of Defense, US Army Promotes innovative, multi-institutional, multidisciplinary, and regionally

focused research directed toward eliminating prostate cancer. Application deadline is May 17, 2000. Information: <http://cdmrp.army.mil> or [cdmrp.pa@det.amedd.army.mil](mailto:cdmrp.pa@det.amedd.army.mil)

***Breast Cancer Research Program*** - Department of Defense, US Army  
This is a multidisciplinary effort aimed at the eradication of breast cancer. Application deadline for letter of intent is May 24, 2000. Application deadline for proposal is June 7, 2000. Information: <http://cdmrp.army.mil> or [cdmrp.pa@det.amedd.army.mil](mailto:cdmrp.pa@det.amedd.army.mil).

## **Mark Kelley, Ph.D. & David Moore, M.D. Receive DOD Grant**

Mark Kelley, Ph.D., Department of Pediatrics and Biochemistry and Molecular Biology, and David Moore, M.D., Department of OB/GYN have received a three year grant from the Army entitled, "Expression of the DNA Repair/Redox Enzyme APE/REF-1 in Epithelial Ovarian Cancers: Diagnostic, Mechanistic and Therapeutic Studies." They will study whether there is a difference in APE/ref-1 function with respect to the extent of ovarian cancer (early versus advanced stage), the process of cancer spread (ovarian tumor versus metastatic tumor), the responsiveness of the cancer to chemotherapy, and finally the exposure to chemotherapy (before versus after). Through these analyses, it will be determined whether APE/ref-1 plays a key role in the spread of ovarian cancer cells and whether APE/ref-1 influences the likelihood ovarian cancer cells can be killed with conventional chemotherapy. Furthermore, they intend to study the underlying mechanisms (DNA repair, reduction-oxidation regulation) by which APE/ref-1 function is linked to the development and progression of ovarian cancer. It is believed that this research can lead to treatment strategies based on genetic manipulations of APE/ref-1 function as well as strategies for the primary prevention of ovarian cancer.

## **Ovarian Cancer Research Committee**

A small group of people have begun meeting monthly to begin a collaboration for the development of collaborative laboratory and translational research in ovarian cancer. Each meeting consists of informal discussion and scientific presentation. The meetings occur on the fourth Wednesday of each month. The next meeting is April 26 at 2:30 pm in the third floor conference room of the Cancer Research Institute. All interested persons are invited. If you plan to attend or have questions, please contact Steve Williams at [stdwilli@iupui.edu](mailto:stdwilli@iupui.edu)

## **Michael Darling Elected President of ACE**

Michael Darling, Associate Director for Administration, for the Indiana University Cancer Center has been elected to the position of President-elect for the Association of Cancer Executives. The association is comprised of academic and community cancer center administrators whose purpose is to improve the administration of the business and non-medical aspects of cancer care.

### **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:

Elizabeth Parsons (eparsons@iupui.edu)  
phone 278-0070 or fax 278-0074