This PDF contains:

(1) A description of what we do, success of past undergrads and who would be reasonable candidate to work with us.
(2) A press release issued by the U. of I. this summer describing some of our work.
(3) A list of 2007-2008 papers and patents from our lab.

To Junior MCB Majors: During the Spring semester, when students inquired about undergraduate research opportunities in our lab we had to decline because of funding and our need to move out of most of our space for renovations. These issues have largely been resolved and we are now interested in talking with with able, motivated and energetic undergraduate research students.

Recent Undergrads in our Lab: The most recent undergrad in our lab, Nicole Patterson delivered a podium talk at the Endocrine Society National Meeting in San Francisco in June, (these talks are usually given by senior postdocs or professors) was author of several papers and is now an MD/Ph.D. student at Washington University Medical School in Saint Louis (Wash. Univ. Med School is generally ranked 3rd in the country (1) Harvard, (2) Johns Hopkins, (3) Wash. U. (4) U. Pennsylvania). The undergrad before Nicole, Hunter Shain is an NSF predoctoral fellow (and Stanford Special Graduate Fellow) At Stanford University. The Undergrad before Hunter, Rebecca Harris is an MD/Ph.D. student at Northwestern Medical School (she turned down MD/Ph.D. at Penn). While these were obviously students with outstanding grade point averages exam scores and activities, their time in our lab, successful research and my enthusiastic support clearly contributed to their success in achieving their goals. We have every reason to anticipate that future undergraduate researchers will be every bit as successful.

What we Do: For many years our lab focused on the mechanisms by which estrogens and other hormones regulated gene expression and mRNA decay in cancer cells. Recently, we have leveraged that expertise by developing a new platform for identifying and then small molecule inhibitors that block the growth of estrogen-dependent breast cancer and androgen (testosterone) dependent prostate cancer. We recently identified the first members of a new class of inhibitors of estrogen receptorinhibitors. Our lead inhibitor TPSF shows great promise in blocking growth of human breast cancer cells that are resistant to current drugs, such as tamoxifen. Nicole's talk and my press conference at the Endocrine meeting received substantial recent recognition and were written up in several major media outlets including the Washington Post and U.S. News and World report. A major focus for undergraduate reserchers will be doing for prostate cancer what we have done for breast cancer. Prostate cancer is totally dependent on androgens and androgen receptor. Unlike reast cancer for which there were some pretty good therapeutic agents, therpaeutic options for recurrent

prostate cancer are very limited. We have the systems up and running and have identified some inhibitors but we want to produce something for androgen dependent prostate cancer as impressive as TPBM is for breast cancer;.

Because we have been so busy, our lab web site has not been updated in a long time and does NOT reflect current research. I therefore include the article and press release that which Diana Yates and I prepared. This was both disseminated to media outlets and published as the lead in Illini Week (July 3, 2008),. This provides a summary of some of the breast cancer work. Also included is a list of our journal articles and patents for 2007-2008.

Who Should Consider Our lab: For those who emailed in the Spring, if you found other labs to work in thats fine. For those still considering a lab: Juniors should have at least 10 hr/week, and preferably around 15 hours a week avalable for lab research, and at least a 3.0 average, and have completed and done well in the the standard MCB and/or Biochemistry courses and labs. Research takes time and students should expect to work in the lab during the academic year and perhaps in the summer and next year. Our recent undergrads. had such great success in part because they worked in the lab for Junior and Senior years. If you think you might be interested in joining our lab, please e-mail me a bit about yourself, including grades in MCB courses, and we will set up a time to talk.

Released: 6/16/08

TEAM DISCOVERS NEW INHIBITORS OF ESTROGEN-DEPENDENT BREAST CANCER CELLS

EMBARGOED FOR RELEASE UNTIL 12 NOON CST (US) JUNE 16 (MONDAY)

CONTACT: Diana Yates, Life Sciences Editor 217-333-5802; diya@uiuc.edu

CHAMPAIGN, Ill. — Researchers have discovered a new family of agents that inhibit the growth of estrogen-dependent breast cancer cells. The finding, described today at a meeting of the Endocrine Society, has opened an avenue of research into new drugs to combat estrogen-dependent breast cancers.

"This cell-based study is exciting because it suggests these compounds are likely to be effective in tumors that remain dependent on estrogen for growth but are resistant to current therapies," said principal investigator David J. Shapiro, a professor of biochemistry in the School of Molecular and Cellular Biology at the University of Illinois.

Although multiple factors contribute to the development of breast cancer, estrogens play a key role in the growth of many tumors. More than 80 percent of breast cancer tumors in women over age 45 are activated by estrogen via a protein called an estrogen receptor. When estrogen binds to the receptor, this "estrogen-receptor complex" latches on to DNA and prompts it to transcribe the RNA blueprints for new proteins that promote cell growth, migration and division.

Current therapies for estrogen-receptor-positive (ER-positive) breast cancers include the use of drugs, such as tamoxifen, that interfere with estrogen's ability to bind to the estrogen receptor. Over time, however, ER-positive breast cancer tumors become resistant to tamoxifen. In some resistant tumors, tamoxifen even begins to act like estrogen and actually stimulates tumor growth.

"Tamoxifen is useful in that it is very effective at blocking recurrence of breast cancer in patients for whom the entire tumor is removed," Shapiro said. "But for patients who still have existing tumors, eventually those tumors will become resistant."

(MORE – ER Complex)

Shapiro's team sought to target other steps in the pathway of estrogen action. Using a technique they developed that can quickly determine whether the target DNA is – or is not – bound by the estrogen-receptor complex, the team was able to screen a long list of potential therapeutic compounds to see if they inhibited the binding of the complex to the DNA. They then tested these agents in ER-positive breast cancer cells.

The team identified several compounds that reduce the binding of estrogen-receptor complex to the regulatory regions of genes that are normally activated by this complex. These agents effectively retarded production of the proteins that promote the growth and proliferation of ER-positive breast cancer cells.

"These small molecules specifically block growth of estrogen-dependent breast cancer cells with little or no effect other cells," Shapiro said. "This work sets the stage for further development and testing of these inhibitors."

The collaboration included researchers from the University of Colorado, the University of North Carolina, and the University of Illinois departments of molecular and integrative physiology and chemistry.

This basic research study was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) at the National Institutes of Health.

-dy-

EMBARGOED FOR RELEASE UNTIL 12 NOON CST (US) JUNE 16 (MONDAY)

Editor's note: To reach David Shapiro, call 217-333-1788; e-mail: djshapir@uiuc.edu.

Shapiro Lab
Papers and Patents (2007-2008)

Mao C, Pattterson NM, Cherian, MT, Aninye IO, Zhang C, Montoya JB, Cheng J, Putt KS, Hergenrother PJ, Wilson EM, Nardulli AM, Nordeen SK and Shapiro DJ (2008) A new small molecule inhibitor of estrogen receptor α binding to estrogen response elements blocks estrogen-dependent growth of cancer cells. *J Biol Chem*., 283: 12819-12830 Online: jbc.org/cgi/content/full/283/19/12819
(Selected for Faculty of 1000 Biology "…that highlights and evaluates the most interesting papers published in the biological sciences, based on the recommendations of over 2000 of the world's top researchers.")

Jiang X, Patterson NM, Ling Y, Xie J, Helferich WG and Shapiro DJ (2008) Low concentrations of the soy phytoestrogen genistein induce proteinase inhibitor 9 and block killing of breast cancer cells by immune cells. *Endocrinology*, In press, On Line 7/31/08

Jiang X, Ellison SJ, Alarid, ET and Shapiro DJ (2007) Interplay between the levels of estrogen and estrogen receptor controls the level of the granzyme inhibitor, proteinase inhibitor 9 and susceptibility to immune surveillance by natural killer cells. *Oncogene*, 26: 4106-4114 Online: nature.com/onc/journal/v26/n28/full/1210197a

Cunningham TD, Jiang X and Shapiro, DJ (2007) Expression of high levels of human proteinase inhibitor 9 blocks both perforin/granzyme and Fas/Fas ligand-mediated cytotoxicity. *Cellular Immunology,* 245:32-41. Online: sciencedirect.com/science/article/B6WCF-4NNYG2D-1/2/e36abded06ba3feb08c0a2b7381da054

Wang S, Zhang C, Nordeen SK, and Shapiro DJ (2007) *In vitro* fluorescence anisotropy analysis of the interaction of full-length SRC1a with estrogen receptors α and β supports an active displacement model for coregulator utilization.
J. Biol. Chem., 282: 2765-2775. Online: jbc.org/cgi/content/full/282/5/2765

Cheng J, Zhang C, and Shapiro DJ (2007) A functional serine 118 phosphorylation site in estrogen receptor-α is required for down-regulation of gene expression by 17β-estradiol and by 4-hydroxytamoxifen. *Endocrinology*, 148: 4634-4641. Online: endo.endojournals.org/cgi/content/full/148/10/4634

Zhou J-H, Yu DV, Cheng J, and Shapiro DJ (2007) Delayed and persistent ERK1/2 activation is required for 4-hydroxytamoxifen-induced cell death. *Steroids*, 72: 765-777. Online: sciencedirect.com/science/article/B6TC9-4P4NPK3 1/2/d95ac32e385f30ef684b4f8d6cbdbfd4

Cheng J, Yu DV, Zhou J-H and Shapiro DJ (2007) Tamoxifen induction of C/EBPα is required for tamoxifen-induced apoptosis. *J. Biol. Chem.* 282: 30535-30543 Online:
jbc.org/cgi/doi/10.1074/jbc.M704829200

Patent Applications 2007-2008

Mao C, Cherian MT and Shapiro, DJ (2008) Compositions and methods related to nuclear hormone receptors and steroid hormone receptors including substituted theophylline inhibitors of estrogen receptor alpha-mediated gene expression. U.S. Provisional Patent Application No. 61/022,126 (filed 01/18/08, amended 06/13/08)