PROFILE
Anna Williams

NSF Graduate Fellow

NSF GK-12 Project:	Northeastern University GK-12-PLUS (Partners Linking Urban Schools) URL: http://www.gk12.neu.edu
Thesis Title:	Progress Toward Breast Cancer Suppression: Development of Novel Antagonists of ER-Coactivator Binding
College/University:	Northeastern University
Research Advisor:	Dr. Robert N. Hanson

Degree Sought
Ph.D.

University Department and/or Lab
Organic Chemistry
Department of Chemistry and Chemical Biology

Research Focus: A proteomimetic approach to antagonism of the estrogen receptor.

Description of Research
The estrogen receptor (ER) is one of a class of nuclear hormone receptors, all of which influence cellular behavior by a similar mechanism of action. A ligand-binding domain initially binds hormones, encouraging dimerization and triggering a conformational change that opens the coactivator binding site. Activation allows the receptor to bind to response elements in DNA, invoking receptor-dependent biological cascades.[1]

Hormone binding to the ER induces a constant cycle of cell proliferation and death in mammary and uterine endometrial tissues, increasing the rate of DNA mutation and therefore the risk of tumor growth.[2] Development of ER antagonists has therefore received major attention in recent years, resulting in the marketing of therapeutics toward the treatment and prevention of breast cancer. However, due to chemical differences in the protein structures, some antagonists of mammary ERs have actually been found to agonize uterine ERs, thereby increasing the likelihood of uterine cancer.[3] For this reason, other methods of ER inhibition are being sought.

We have chosen to employ proteomimetics, or nonpeptidyl molecules that mimic protein conformation and function,[4] in order to mimic the binding of coactivators to the ER. A single α-helical pentapeptide termed the NR-box, consisting of an LXXLL amino acid sequence, governs ER-coactivator binding. The NR-box is oriented within the ER active site by a charge clamp between lysine and glutamic acid residues on the receptor and the polypeptide backbone of the NR-box.[5,6] In recent years, bi- and tri-aryl structures have been demonstrated to mimic α-helices.[7,8] By utilizing a substituted biphenyl scaffold complete with amino and carboxyl termini, we are developing what we anticipate to be a series of potent inhibitors of ER-coactivator binding.

Example of how my research is integrated into my GK-12 experience

It took me until my junior year of college to begin to truly recognize the relevance of academic chemistry to biological and materials research. I think it is very important to integrate evidence of this approach at a younger age. Many students believe that the only way to vocationally exercise their scientific interests is by entering a career in medicine. I want to introduce the concept of research and development on both the academic and industrial level to students, and potentially expose students to a range of fields to which their elementary scientific knowledge may lead them. Although details of organic synthesis is beyond the scope of an AP chemistry course, I hope to introduce them to the logical creativity that underscores the field.

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[1] Geistlinger TR, Guy RK. *Methods Enzymol.* 2003, *364*, 223-246
[2] Kushner PJ, Webb P, Uht RM, Liu MM, Price RH. *Pure Appl. Chem.* 2003, *75*, 1757-1769.
[3] Bryant HU. *Reviews in Endocrine & Metabolic Disorders.* 2002. *3*, 231-241
[4] Davis JM, Tsou LK, Hamilton AD. *Chem Soc Rev.* 2007, *36*, 326-334.
[5] Savkur RS, Burris TP. *J Peptide Res.* 2004, *63*, 207-212
[6] Nettles KW, Greene GL. *Annu Rev Physiol.* 2005, *37*, 309-333.
[7] Fletcher S, Hamilton AD. *Curr Opin Chem Biol.* 2005, *9*, 632-638.
[8] Garner J, Harding MM. *Org Biomol Chem.* Published online 09/07/2007, **DOI:** 10.1039/b710425a.