BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Graves, Lee M.	**Professor**
eRA COMMONS USER NAME lee_m_graves	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Iowa State University, Ames, IA	B.S.	1982	Biochemistry
University of Illinois, Urbana, IL	Ph.D.	1990	Biochemistry
University of Washington, Seattle, WA	Postdoc	1994	Pharmacology

A. Personal Statement

I have over 25 years' experience studying protein kinases, protein kinase inhibitors, and protein phosphorylation. I have a long-standing interest in studying protein-protein interactions, protein kinases, and their regulation in cancer. The overall objective of my research is to develop and apply novel affinity approaches to study dysregulation of protein kinases in disease. This includes applying novel technologies such as kinase inhibitor bead affinity chromatography (MIBs), protein-protein interactions, titanium and phosphotyrosine peptide capture, methods of quantitative mass spectrometry and advanced bioinformatics. I am developing a new chemical biology, affinity chromatography methodology for integrated kinome capture (MIBs) and targeted MS approach (MRM) to specifically quantitate select members of the kinome. Using the MIBs profiling provides a novel approach to study changes in the kinome 'en masse'. I am particularly interested in developing additional affinity-based chemical biology methods to apply to drug discovery and biology. Thus I am uniquely qualified to perform studies to study the kinome of multiple cancers. In addition to running a research lab and directing the UNC Proteomics Facility, I am the Director of Graduate Studies for Pharmacology. I have mentored a large number of undergraduate, graduate and post-doctoral fellows including students from the SURE and Partners programs. Thus I am well qualified to perform the proposed research and to mentor students involved in MS and Ph.D training programs.

B. Positions and Honors

Positions and Employment

1990-1994 Postdoctoral Research Fellow (w/ Dr. Edwin G. Krebs), Department of Pharmacology University of Washington, Seattle, WA
1994-1995 Lecturer, Department of Pharmacology, University of Washington, Seattle, WA
1995-2001 Assistant Professor, Dept. of Pharmacology, University of NC at Chapel Hill, Chapel Hill, NC
2001-2013 Associate Professor, Dept. of Pharmacology, University of NC at Chapel Hill, Chapel Hill, NC
2014-present Professor, Dept. of Pharmacology, University of NC at Chapel Hill, Chapel Hill, NC

Other Experience and Professional Memberships

2000-present American Society for Pharmacology and Experimental Therapeutics (ASPET)
2002-present American Society for Biochemistry and Molecular Biology (ASBMB)
2013- present NIH Study Section (MIST)- permanent member

Honors

2000 Jefferson-Pilot Research Award - University of North Carolina
2000 American Heart Association Established Investigator Award - University of North Carolina
2006 PHRMA Sabbatical Fellowship Award-University of North Carolina
2007 University of Sydney International Research Fellowship

C. Contributions to Science

1. Application of Proteomics/Metabolomics to Study Drug Resistance in Leukemia

We have focused on developing methods to investigate the molecular basis of drug resistance in leukemias. This research has been a multi-tiered approach to elucidate metabolic, phosphorylation and miRNA-dependent mechanisms broadly contributing to multi-drug resistance. This effort overlaps with contribution #2 which is to develop methods to study kinase changes in disease. The following publications reflect our efforts:

1. Zimmerman E.I., Leisewitz A. V., Huang M., Yang J., and **Graves L.M**. Identification of a Novel Point Mutation in ENT1 that Confers Resistance to Ara-C in Human T cell Leukemia CCRF-CEM Cells. *FEBS Lett.* 583(2):425-9. Epub 2008 Dec 29 (2009). PMCID:PMC2647365
2. Dewar, B.J., Keshari K., Jeffries R., Dzeja P., **Graves L.M.***, Macdonald J.M* (*Co-senior authors) Metabolic Assessment of a Novel Chronic Myelogenous Leukemic Cell Line and an Imatinib Resistant Subline by 1H NMR Spectroscopy. *Metabolomics* 6(3):439-450. Epub 2010 Mar 2 (2010). PMCID:PMC2899017
3. Wang, Q., Zimmerman E.I., Toutch A., Martin T.D., **Graves L.M.**, and Lawrence D.S. Multicolor Monitoring of Dysregulated Protein Kinases in Chronic Myeloid Leukemia. *ACS Chemical Biology* 17;5(9):887-9 (2010). PMCID:PMC2943031
4. Zimmerman E.I., Dollins C.M., Crawford M., Grant S., Nana-Sinkam S.P., Richards K.L., Hammond S.M., and **Graves L.M.** Lyn Kinase-dependent Regulation of miR181b and Mcl-1 Expression: Implications for Drug Resistance in Myelogenous Leukemia. *Molecular Pharmacology*, 78 (5): 811-817 (2010). PMCID:PMC2981365

2. Kinome Remodeling in Response to Disease or Drug Exposure

We have collaborated with Dr. Gary Johnson to develop novel methodologies to study the kinome (collection of 518 kinases) en masse. Our labs developed multiplexed inhibitor bead (MIB) mass spectrometry (MS) as a novel approach to capture, identify and quantitate active kinases from any sample. We applied this to study drug- resistant leukemias as well as drug responses in breast cancer. This is a major effort of our current research and we are applying this technology to a variety of cancer projects.

1. Duncan J.S., Whittle M.C., Nakamura K., Abell A.N., Midland A.A., Zawistowski J.S., Johnson N.L., Granger D.A., Jordan N.V., Darr D.B., Usary J., Kuan P-F., Smalley D.M., Major B., He X., Hoadley K., Sharpless N.E., Perou C.M., Gomez S.M., Chen X., Jin J., Frye S.V., Earp H.S., **Graves L.M.**, and Johnson G.L. Dynamic Reprogramming of the Kinome In Response to Targeted MEK Inhibition In Triple Negative Breast Cancer. *Cell* 149(2), 307-321 (2012). PMCID: PMC3328787
2. Cooper M.J., Cox, C.N., Zimmerman E.I., Dewar B.J., Duncan J.S., Whittle M.C., Nguyen T., Jones L., Ghoseroy S., Smalley D., Kuan P-F., Richards K.L., Christopherson R.I., Jin J., Frye S.V., Johnson G.L., Baldwin A.S., and **Graves L.M.** (2013) Application of Multiplexed Kinase Inhibitor Beads to Study Kinome Adaptations in Drug Resistant Leukemia *PLOS One* 8(6), e66755 (2013). PMID: 23826126.
3. **Graves L.M**., Duncan, J.S., Whittle M.C., and Johnson G.L. The Dynamic Nature of the Kinome. *Bioch. J*. 450 (1), 1-8 (2013). PMID: 2334319
4. Stuhlmiller TJ, Miller SM, Zawistowski JS, Nakamura K, Beltran AS, Duncan JS, Angus SP, Collins KA, Granger DA, Reuther RA, **Graves LM**, Gomez SM, Kuan PF, Parker JS, Chen X, Sciaky N, Carey LA, Earp HS, Jin J, Johnson GL. Inhibition of Lapatinib-Induced Kinome Reprogramming in ERBB2-Positive Breast Cancer by Targeting BET Family Bromodomains. *Cell Rep.* 2015 Apr 21;11(3):390-404. PMID: 25865888

3. Regulation of Metabolic Enzymes by Phosphorylation

We have a long-standing interest in identifying phosphorylation events in metabolic enzymes that dictate their properties. We have focused on enzymes involved in pyrimidine (CTP) biosynthesis- since this is a rate-limiting process. Our publications on the human CTPS 1 and 2, were the first to characterize the phosphorylation dependent regulation of this enzyme in human cells.

1. Huang, M., Wang, Y.H., Collins, M.A., and **Graves, L.M**. (2004). CPEC Induces Erythroid Differentiation of K562 Cells Through CTP Depletion and Activation of p38 MAP Kinase. *Leukemia* 18, 1857-1863. PMID: 15385935.

2. Higgins M.J., Graves P.R., and **Graves L.M.** (2007). Regulation of Human Cytidine Triphosphate Synthetase 1 by Glycogen Synthase Kinase 3 Beta. *J. Biol Chem*, 282(40), 29493-29503. PMID: 17681942.
3. Higgins M.J., Loiselle D., Haystead, T.A., and **Graves L.M**. (2008). Human Cytidine Triphosphate Synthetase 1 Interacting Proteins. *Nucleosides, Nucleotides and Nucleic Acids 27, 850-857.* PMID: 20739275.
4. Kassel K.M., Au D.R., Higgins, M.J., Hines M., and **Graves, L.M**. (2010). Regulation of Human Cytidine Triphosphate Synthetase 2 by Phosphorylation. *J. Biol Chem.* 285 (44): 33727-33336. PMID: 20739275.

4. Proteomics and the Regulation of Transcription, RNA Splicing and Caspase Activity

We have collaborated with a number of groups to apply proteomics to better understand the regulation of multiple cellular processes. This is an active area of research that interfaces with my position as Faculty Director of UNC Proteomics. Shown are examples of recent advances.

1. Duncan J.S., Gyenis L., Lenehan J., Bretner M., **Graves L.M.**, Haystead T.A., Litchfield D.W. An unbiased evaluation of CK2 inhibitors by chemo-proteomics: Characterization of Inhibitor Effects on CK2 and Identification of Novel Inhibitor Targets. *Mol. and Cell Proteomics* 7(6), 1077-1088 (2008). PMID:18258654
2. Beltran A.S., **Graves L.M**., and Blancafort P. (2013). Novel Role of Engrailed 1 as a Prosurvival Transcription Factor in Basal-like Breast Cancer and Engineering of Interference Peptides Block its Oncogenic Function. *Oncogene,* (Oct 31), p1-11. PMID: 24141779.
3. Choudhury R., Roy S.G., Tsai Y.S., Tripathy A., **Graves L.M.**, and Wang Z. (2014). The Splicing Activator DAZAP1 Integrates Splicing Control in MEK/ERK-Regulated Cell Proliferation and Migration. *Nature Comm*. 23(5), 3078. PMID: 24452013
4. Turowec J.P., Zukowski S.A., Knight J.D., Smalley D.M., **Graves L.M**., Johnson G.L., Li S.S., Lajoie G.A., and Litchfield D.W. (2014). An Unbiased Proteomic Screen Reveals Caspase Cleavage is Positively and Negatively Regulated by Substrate Phosphorylation. *Mol Cell Proteomics* 13(5): 1184-97. PMID: 24556848

Complete List of Publications (157)

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