

BIOGRAPHICAL SKETCH

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NAME: Graves, Lee M.

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POSITION TITLE: Professor

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	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, cell signaling and applying proteomics to investigate mechanisms of drug action in cancer. The overall objective of my research is to develop and apply affinity and global proteomics methods to specifically identify cellular mechanisms in a proteome-wide manner. This includes technologies such as kinase inhibitor bead affinity chromatography (MIBs), proximity ligation (BioID) protein-protein interactions, titanium and phosphotyrosine peptide capture, immobilized pharmacophore target capture and methods of quantitative mass spectrometry (MS). Recently, using an immobilized ONC201 analog affinity column, we applied proteomics and discovered ClpP as a novel drug target for ONC201 and related compounds (Graves *et al.*, 2019). This work was recently highlighted in the Scientist and forms the basis of our studies to investigate the biological activities of potent activators of ClpP in cancer (<https://www.the-scientist.com/news-opinion/found--a-cancer-drugs-mechanism-of-action-65918>). We are continuing to investigate the mechanism of action of these novel ClpP activators, particularly on drug-resistant cancer models and establishing the relationship of immune recruitment.

My lab is extensively using MIB/MS profiling to examine changes in the kinome 'en masse' from kinase inhibitor-treated cells, Ras knockdown cells, virally infected cells and brain samples. We are combining these studies with a comprehensive analysis of kinase activities and protein phosphorylation through bioinformatics and statistics. Our lab, working in collaboration with the Moorman lab, was the first to apply MIB/MS kinome profiling to study the effects of HCMV infection on the host kinome (Arend *et al.*, 2017). We have also used this approach combined with phosphoproteomics approach to identify anti-apoptotic proteins (Okumu *et al.*, 2017), to identify drug targets and elucidate mechanisms of kinome adaptation in drug resistance (Krulik *et al.*, 2018; Cann *et al.*, 2019; Blake *et al.*, 2019; Kuciauskas *et al.*, 2019). I am the Faculty Director of UNC Proteomics Core and I work with multiple groups (co-PI on multiple grants) to solve complex kinase and cell signaling problems. As a result of these interactions, I have built a network of collaborations with other Core directors, cancer researchers, immunologists, biochemists and statisticians that support my research. For these reasons, I am very well qualified to lead the Core B Proteomics efforts to study host kinome and phosphoproteome responses in virally-infected cells.

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, Director of Graduate Studies, 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
2017-present Executive Editor, BBA- General Subjects

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. Contribution to Science

https://www.ncbi.nlm.nih.gov/sites/myncbi/10SUdZzZZtwA_/bibliography/44069391/public/?sort=date&direction=descending

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

We have focused on developing methods to investigate the molecular basis of drug resistance in cancer. This research has been a multi-tiered approach to elucidate metabolic, phosphorylation and other 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. Okumu D.O., East M.P., Levine M., Herring L.E., Zhang R., Gilbert T.S.K., Litchfield D.W., Zhang Y., **Graves L.M.** BIRC6 mediates imatinib resistance independently of Mcl-1. *PLoS One*. 2017, May 16;12(5):e0177871. PMID: 28520795
2. Cann ML, Herring LE, Haar L, Gilbert TSK, Goldfarb D, Richards KL, **Graves LM**, Lawrence DS. Dasatinib is preferentially active in the activated B-cell subtype of diffuse large B-cell lymphoma. *J Proteome Res*. 2018, Dec 12. doi: 10.1021/acs.jproteome.8b00841. PMID:30540191
3. Kuciauskas D, Dreize N, Ger M, Kaupinis A, Zemaitis K, Stankevicius V, Suziedelis K, Cicenias J, **Graves LM**, Valius M. Proteomic Analysis of Breast Cancer Resistance to the Anticancer Drug RH1 Reveals the Importance of Cancer Stem Cells. *Cancers* (Basel). 2019, Jul 11;11(7). pii: E972. doi: 10.3390/cancers11070972. PMID: 31336714
4. Okumu DO, Aponte-Collazo LJ, Dewar BJ, Cox NJ, PhD;, East MP, Tech K, McDonald IM, Tikunov AP, Holmuhamedov E, **Graves LM**. Lyn regulates creatine uptake in an imatinib-resistant CML cell line. *BBA- General Subjects* 2019, Dec 24;1864(4):129507. PMID: 31881245.

2. Kinome Remodeling in Response to Disease or Drug Exposure

We are applying global methodologies to study the kinome *en masse*. Our lab uses multiplexed inhibitor bead (MIB) mass spectrometry (MS) as a powerful approach to capture, identify and quantitate active kinases from any sample. We have applied this to study drug-resistant leukemias as well as drug responses in breast and pancreatic cancer. This is a major effort of our current research and we are applying this technology to a variety of cancer projects.

1. Duncan JS, Whittle MC, Nakamura K, Abell AN, Midland AA, Zawistowski JS, Johnson NL, Granger DA, Jordan NV, Darr DB, Usary J., Kuan P-F., Smalley DM, Major B, He X, Hoadley K, Sharpless NE, Perou CM, Gomez SM, Chen X, Jin J, Frye SV, Earp HS, **Graves LM**, and Johnson GL. Dynamic Reprogramming of the Kinome In Response to Targeted MEK Inhibition In Triple Negative Breast Cancer. *Cell* 2012,149(2), 307-321. PMID: 22500798
2. Cooper MJ, Cox, CN, Zimmerman EI, Dewar BJ, Duncan JS, Whittle MC, Nguyen T, Jones L, Ghoseroy S, Smalley D, Kuan P-F, Richards KL, Christopherson RI, Jin J, Frye SV, Johnson GL, Baldwin AS, and **Graves LM**. Application of Multiplexed Kinase Inhibitor Beads to Study Kinome Adaptations in Drug Resistant Leukemia *PLOS One* 2013, 8(6), e66755. PMID: 23826126.

3. Collins KAL, Stuhlmiller TJ, Zawistowski JS, East MP, Pham TT, Hall CR, Goulet DR, Bevill SM, Angus SP, Velarde SH, Sciaky N, Oprea TI, **Graves LM**, Johnson GL, Gomez SM. Proteomic analysis defines kinase taxonomies specific for subtypes of breast cancer. *Oncotarget*. 2018, Jan 29;9(21):15480-15497. PMID: 29643987
4. Krulik J.K., McDonald I.M., Lee B., Okumu D.O., East M.P., Gilbert T.S.K., Herring L.E., Golitz B.T., Wells, C.I., Axtman A.D., Zuercher W.J., Willson T.M., Kireev D., Yeh J.J., Johnson G.L., Baines A.T., and **Graves LM**. Application of Integrated Drug Screening/ Kinome Analysis to Identify Inhibitor of Gemcitabine Resistant Pancreatic Cancer Cell Growth. *SLAS Discovery* 2018, 23(8), 850-861, PMID: 29742358.

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. Higgins M.J., Graves P.R., and **Graves L.M.** Regulation of Human Cytidine Triphosphate Synthetase 1 by Glycogen Synthase Kinase 3 Beta. *J. Biol Chem*, 2007, 282(40), 29493-29503. PMID: 17681942.
2. Higgins M.J., Loiselle D., Haystead, T.A., and **Graves L.M.** Human Cytidine Triphosphate Synthetase 1 Interacting Proteins. *Nucleosides, Nucleotides and Nucleic Acids* 2008, 27, 850-857. PMID: 20739275.
3. Kassel K.M., Au D.R., Higgins, M.J., Hines M., and **Graves, L.M.** Regulation of Human Cytidine Triphosphate Synthetase 2 by Phosphorylation. *J. Biol Chem*. 2010, 285 (44): 33727-33336. PMID: 20739275.
4. McDonald IM, Grant GD, East MP, Gilbert TSK, Wilkerson EM, Goldfarb D, Beri J, Herring LE, Vaziri C, Cook JC, Emanuele MJ, and **Graves LM**. Mass spectrometry-based selectivity profiling reveals a highly selective MELK inhibitor that causes delayed mitotic entry in cells. *J Biol Chemistry* 2020, Jan 2, RA119.011083. PMID: 31896573.

4. Proteomics and the Regulation of Cellular Functions in Viral Infection and Cancer

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 and is supported by a number of funded proposals.

1. Arend KC, Lenarcic EM, Vincent HA, Rashid N, Lazear E, McDonald IM, Gilbert TSK, East MP, Herring LE, Johnson GL, **Graves LM***, Moorman NJ*. Kinome Profiling Identifies Druggable Targets for Novel HCMV Antivirals. *Mol Cellular Proteomics* 2017, Apr16, S263-S276, PMID: 28237943. (*co-senior authors)
2. Vaseva AV, Blake DR, Gilbert TSK, Ng S, Hostetter G, Azam SH, Ozkan-Dagliyan I, Gautam P, Bryant KL, Pearce KH, Herring LE, Han H, **Graves LM**, Witkiewicz AK, Knudsen ES, Pecot CV, Rashid N, Houghton PJ, Wennerberg K, Cox AD, Der CJ. KRAS Suppression-Induced Degradation of MYC Is Antagonized by a MEK5-ERK5 Compensatory Mechanism. *Cancer Cell*. 2018, Nov 12;34(5):807-822.e7. doi: 10.1016/j.ccell.2018.10.001.PMID: 30423298
3. Blake DR, Vaseva AV, Hodge RG, Kline MP, Gilbert TSK, Tyagi V, Huang D, Whiten GC, Larson JE, Wang X, Pearce KH, Herring LE, **Graves LM**, Frye SV, Emanuele MJ, Cox AD, Der CJ. Application of a MYC degradation screen identifies sensitivity to CDK9 inhibitors in KRAS-mutant pancreatic cancer. *Sci Signal*. 2019, 12(590). PMID: 31311847
4. Graves PR, Aponte-Collazo LJ, Fennell EMJ, Graves AC, Hale AE, Dicheva N, Herring LE, Gilbert TSK, East MP, McDonald IM, Lockett MR, Ashamalla H, Moorman NJ, Karanewsky DS, Iwanowicz EJ, Holmuhamedov E and **Graves LM**. Mitochondrial Protease ClpP is a Target for the Anticancer Compounds ONC201 and Related Analogues. *ACS Chem Biol*. 2019, May 1. doi: 10.1021/acscchembio.9b00222. PMID: 31021596.