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. 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). My lab has used MIB/MS profiling to examine the kinome from kinase inhibitor-treated cells, Ras knockdown cells, virally infected cells, and brain samples. We combine 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 cancer drug resistance (Vaseva *et al*., 2018, Krulikas *et al.,* 2018; Cann *et al.,* 2019; Blake *et al.,* 2019; Kuciauskas *et al.,* 2019, McDonald *et al.* 2020, Lipner *et al*., 2020). Most recently we have completed the MIB-MS kinome analysis of Raf and Ras inhibition (Water *et al*., 2021, Ozkan-Dagliyan *et al.,* 2020).

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 my lab's studies to investigate the biological activities of potent activators of ClpP in cancer. As part of my RO1, we are continuing to investigate the mechanism of action of these novel ClpP activators on the proteome, phosphoproteome, metabolome and transcriptome. These multi-omic analyses are already revealing important insights into the mechanism of action of these exciting new class of anti-cancer compounds.

I am also the Faculty Director of UNC Proteomics Core, and I direct a large group of scientists to apply proteomics to biological research. As a result, I have built a network of collaborations with other Core directors, cancer researchers, virologists, immunologists, biochemists, and statisticians. I work with multiple groups (co-PI on multiple grants) to solve complex kinase and cell signaling problems. We perform MIB-MS kinome profiling, phosphoproteomics and protein-protein interactions studies using the latest cutting edge mass spectrometers and technology. Thus, I am well qualified to contribute to kinome profiling and proteomics studies as described in this proposal.

Highlighted Funding

1R01GM138520-01 (Graves-PI)
09/15/2020-06/30/2024
Elucidating the mechanism of action of novel ClpP activators in activation of the mitochondrial unfolded protein response

R35 CA232113 (Der)
09/01/2018-08/31/2025
Targeting undruggable RAS for cancer treatment

R37-CA251877 (Bryant)
07/01/2020 - 06/30/2025
Mechanistic dissection and inhibitor targeting of autophagy in RAS driven cancers

R01AI152092 (Chibale, Ferrins, Willson)
04/03/2020 - 03/31/2025
Repurposing kinase inhibitor chemotypes as antimalarials

1R01CA247436-01A1 (Dotti)
01/01/2021 - 12/31/2025
Tuning CAR-T Cell Functions

1U01TR003715-01 (Hingtgen)
04/01/2021-03/31/2025
A consortium effort to translate therapies for neurological diseases via an ex vivo organotypic platform

R01 CA199064 (Yeh)
08/01/2016-07/31/2021
Tumor subtypes and therapy response in pancreatic cancer

B. Positions and Honors

Positions and Employment

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

Other Experience and Professional Memberships

2017-present	Executive Editor, BBA- General Subjects
2013- present	NIH Study Section (MIST)- permanent member
2002-present	American Society for Biochemistry and Molecular Biology (ASBMB)
2000-present	American Society for Pharmacology and Experimental Therapeutics (ASPET)

Honors

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

C. Contribution to Science

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, Cicenas 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, East MP, Tech K, McDonald IM, Tikunov AP, Holmuhamedov E, Macdonald JM, **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. Krulikas 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/acschembio.9b00222. PMID: 31021596.