BIOGRAPHICAL SKETCH

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NAME: Graham, Nicholas Alexander

eRA COMMONS USER NAME (credential, e.g., agency login): NGRAHAM2

POSITION TITLE: Assistant 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
Washington University in St. Louis (St. Louis, MO)	B.S.	05/2001	Chemical Engineering & French
California Institute of Technology (Pasadena, CA)	M.S.	06/2004	Chemical Engineering
California Institute of Technology (Pasadena, CA)	Ph.D.	06/2007	Chemical Engineering
Simon Fraser University (Burnaby, BC, Canada)	Postdoc	08/2007	Molecular Biology & Biochemistry
University of California, Los Angeles	Postdoc	07/2013	Medical & Molecular Pharmacology

A. Personal Statement

My training in both *quantitative sciences* (chemical engineering), *pathway biology* (graduate studies) and *systems biology* (postdoctoral training) has provided me with the broad expertise required to carry out research related to cancer signaling and metabolism. The overarching theme of my research program is to generate quantitative, interconnected *systems* models of cancer in order to improve clinical care. Drawing on biology, statistics and computation, my research aims to develop and use quantitative models for design and evaluation of new therapeutic modalities. We are particularly interested in using high resolution mass spectrometry to probe the kinase-mediated signaling pathways (ie, phospho-proteomics) and metabolic flux (ie, metabolomics) in cancer cells.

My postdoctoral work focused on using systems approaches to cancer biology in collaboration with physician scientists including Antoni Ribas (UCLA Hematology-Oncology) and Owen Witte (UCLA Microbiology, Immunology & Molecular Genetics). Membership in the Norris Comprehensive Cancer Center will allow me to build similar collaborations with physician scientists and oncologists to enable translation of findings from research projects into the clinic.

1. **Graham NA**, Tahmasian M, Kohli B, Komisopoulou E, Zhu M, Vivanco I, Teitell MA, Wu H, Ribas A, Lo RS, Mellinghoff IK, Mischel PS, and Graeber TG (2012). Glucose deprivation activates a metabolic and signaling amplification loop leading to cell death. *Molecular Systems Biology*, 8:589. PMCID: PMC3397414 (profiled in accompanying News & Views)
2. Drake JM, **Graham NA**, Stoyanova T, Sedghi A, Goldstein AS, Cai H, Smith DA, Zhang H, Komisopoulou E, Huang J, Graeber TG, and Witte ON (2012). Oncogene-specific activation of tyrosine kinase networks during prostate cancer progression. *Proceedings of the National Academy of Sciences (USA)*, 109(5), 1643-8. PMCID: PMC3277127
3. Sun J*, Masterman-Smith M*, **Graham NA***, Jiao J*, Mottahedeh J, Laks DR, Ohashi M, DeJesus J, Kamei K, Lee KB, Wang H, Yu ZT, Lu YT, Hou S, Li K, Liu M, Zhang N, Wang S, Angenieux B, Panosyan E, Samuels ER, Park J, Williams D, Konkankit V, Nathanson D, van Dam RM, Phelps ME, Wu H, Liau LM,

Mischel PS, Lazareff JA, Kornblum HI, Yong WH, Graeber TG and Tseng HR (2010). A microfluidic platform for systems pathology: multiparameter single-cell signaling measurements of clinical brain tumor specimens. *Cancer Research*, 70(15), 6128-38. PMCID: PMC3163840 (***denotes equal contribution**)

4. **Graham NA** and Asthagiri AR (2004). EGF-mediated Tcf/Lef transcriptional activity is essential, but not sufficient, for cell cycle progression in non-transformed mammary epithelial cells. *The Journal of Biological Chemistry*, 279(22), 23517-24.

B. Positions and Honors

Positions and Employment

2001-2004	National Defense Science and Engineering Graduate Research Fellow, Dept. Chemical Engineering, Caltech (PI: Dr. Anand R. Asthagiri)
2004-2007	Graduate Student Researcher, Dept. Chemical Engineering, Caltech (PI: Dr. Anand R. Asthagiri)
2006	NSF East Asia and Pacific Summer Institute, Dept. of Biotechnology, Yonsei University, Seoul, South Korea (PI: Dr. Kang-Yell Choi)
2007	Visiting Postdoctoral Fellow, Dept. Molecular Biology and Biochemistry, Simon Fraser University, Burnaby, British Columbia, Canada (PI: Dr. Dipankar Sen)
2007-2008	Postdoctoral Scholar in Oncologic Molecular Imaging, Dept. Medical and Molecular Pharmacology, UCLA (PI: Dr. Thomas G. Graeber)
2008-2012	Postdoctoral Fellow in Tumor Cell Biology, Dept. Medical and Molecular Pharmacology, UCLA (PI: Dr. Thomas G. Graeber)
2012-2013	Postdoctoral Scholar in Oncologic Molecular Imaging, Dept. Medical and Molecular Pharmacology, UCLA (PI: Dr. Thomas G. Graeber)
2013-2014	Assistant Project Scientist, Dept. Medical and Molecular Pharmacology, UCLA (PI: Dr. Thomas G. Graeber)
2015-	Assistant Professor, Dept. of Chemical Engineering and Materials Science, University of Southern California

Other Experience and Professional Memberships

1998-2001	Tau Beta Pi Engineering Honor Society, Washington University
2005-2007	Biophysics Lecture Series Planning Committee, Caltech
2008-2014	Guest lecturer, Introduction to Molecular Imaging, Dept. Medical and Molecular Pharmacology, UCLA
2008-	Reviewer for *Nature Biotechnology*, *Nature Communications*, *PLoS Computational Biology*, *PLoS One* and *Molecular Systems Biology*, *BBA Molecular Cell Research* (with Thomas Graeber and Heather Christofk, UCLA)
2011-2012	Lab assistant for American Association for Cancer Research's *Molecular Biology in Clinical Oncology* workshop
2015	Co-Lab Director for American Association for Cancer Research's *Molecular Biology in Clinical Oncology* workshop

Honors

1997	Tandy Technology Scholar, Tandy Corporation
1997-2001	National Merit Scholar, Honeywell Foundation
1997-2001	Stanley C. Pace Undergraduate Fellowship, School of Engineering and Applied Science, Washington University
2000	Klemm Outstanding Junior Award, Dept. Chemical Engineering, Washington University
2001	Procter & Gamble Senior Scholar Award, Dept. Chemical Engineering, Washington University
2001	Magna Cum Laude, Washington University
2001-2004	National Defense Science and Engineering Graduate Fellowship
2004	Dow Travel Fellowship, Division of Chemistry and Chemical Engineering, Caltech
2005	Honorable Mention Oral Presentation Award, UCLA Biomedical Engineering Conference
2006	NSF East Asia and Pacific Summer Institute, Yonsei University, Seoul, Korea
2011	Most Outstanding Oral Presentation, UCLA Medical and Molecular Pharmacology Annual Retreat

2011 Axel Ullrich Scholar-in-Training award, AACR-NCI Conference on Systems Biology
2013 Best postdoctoral poster, UCLA Dept. Molecular and Medical Pharmacology Annual Retreat
2013 Best postdoctoral oral presentation, Crump Institute for Molecular Imaging Research Seminar

C. Contribution to Science

1. Copy number alteration (CNA) profiling of human tumors has revealed recurrent patterns of DNA amplifications and deletions across diverse cancer types. These patterns are suggestive of conserved selection pressures during tumor evolution, but cannot be fully explained by known oncogenes and tumor suppressor genes. During my postdoctoral studies, I have led a pan-cancer analysis of CNA data from patient tumors and experimental systems to show that principal component analysis-defined CNA signatures are predictive of glycolytic phenotypes, including FDG-avidity of patient tumors, and increased proliferation. A cross-species comparison of CNA identified 21 conserved altered DNA regions containing 13 enzymes in the glycolysis and pentose phosphate pathways in addition to known cancer driving genes. Furthermore, exogenous expression of hexokinase and enolase enzymes in an experimental immortalization system altered the copy number status of the corresponding endogenous loci, supporting the hypothesis that these metabolic genes act as drivers within the conserved CNA amplification regions. These results demonstrate that metabolic stress acts as a selective pressure underlying the recurrent CNAs observed in human tumors, and further cast genomic instability as an enabling event in tumorigenesis and metabolic evolution. This co-first author work is currently under review at *Cell Systems*.

2. The metabolic state of cancer cells has generally been assumed to be driven by intracellular signaling pathways (eg, insulin signaling drives glucose uptake). In cancer cell lines dependent on glucose for survival, I demonstrated that the signaling-metabolism interactions are in fact bi-directional, or that the metabolic state of cells can drive intracellular tyrosine kinase signaling. Using quantitative, label-free mass spectrometry, I elucidated a signaling and metabolism positive feedback loop that regulates cell death following glucose withdrawal. This positive feedback loop involves reactive oxygen species (ROS)-mediated inhibition of protein tyrosine phosphatases, which causes increased tyrosine kinase signaling, thereby inducing further ROS generation until cells undergo ROS-mediated cell death. This work has led to more detailed understanding of how signaling and metabolism are interconnected in cancer.

    a. **Graham NA**, Tahmasian M, Kohli B, Komisopoulou E, Zhu M, Vivanco I, Teitell MA, Wu H, Ribas A, Lo RS, Mellinghoff IK, Mischel PS, and Graeber TG (2012). Glucose deprivation activates a metabolic and signaling amplification loop leading to cell death. *Molecular Systems Biology*, 8:589. PMCID: PMC3397414 (profiled in accompanying News & Views)

3. With a team of collaborators, I have led the development of bioinformatic techniques to analyze genome-wide RNA expression data and multiparameter, single-cell signaling measurements. In collaboration with a microfluidics lab and brain tumor clinicians, I adapted a machine learning technique called self-organizing maps (SOM) to analyze multiparameter, single-cell data from brain tumor biopsies. This work demonstrated that molecular signatures from only 2,000 cells can be predictive of clinical phenotype. In collaboration with Heather Christofk, PhD, I used RNA microarray data to uncover a novel mechanism by which viral infection promotes host cell glycolysis. For these projects, I led the bioinformatic analysis.

    a. Sun J*, Masterman-Smith M*, **Graham NA***, Jiao J*, Mottahedeh J, Laks DR, Ohashi M, DeJesus J, Kamei K, Lee KB, Wang H, Yu ZT, Lu YT, Hou S, Li K, Liu M, Zhang N, Wang S, Angenieux B, Panosyan E, Samuels ER, Park J, Williams D, Konkankit V, Nathanson D, van Dam RM, Phelps ME, Wu H, Liau LM, Mischel PS, Lazareff JA, Kornblum HI, Yong WH, Graeber TG and Tseng HR (2010). A microfluidic platform for systems pathology: multiparameter single-cell signaling measurements of clinical brain tumor specimens. *Cancer Research*, 70(15), 6128-38. PMCID: PMC3163840 (***denotes equal contribution**)

    b. Thai M, **Graham NA**, Braas D, Nehil M, Komisopoulou E, Kurdistani SK, McCormick F, Graeber TG and Christofk HR (2014). Adenovirus E4ORF1-induced MYC activation promotes host cell anabolic glucose metabolism and virus replication. *Cell Metabolism*, 19(4), 694-701. PMCID: PMC4294542

    c. Hong CS, **Graham NA**, Gu W, Camacho CE, Mah V, Maresh EL, Alavi M, Bagryanova L, Krotee PAL, Gardner BK, Behbahan IS, Horvath S, Chia D, Mellinghoff IK, Hurvitz SA, Dubinett SM, Critchlow SE, Kurdistani SK, Goodglick L, Braas D, Graeber TG, Christofk HR (2016). MCT1

modulates cancer cell pyruvate export and growth of tumors that co-express MCT1 and MCT4. *Cell Reports*, 14(7):1590-601. PMCID: PMC4816454

4. Prostate cancers generally lack mutated or amplified tyrosine kinases and are therefore not treated with tyrosine kinase inhibitors (eg, dasatinib). In collaboration with a prostate cancer lab, I have measured and analyzed global phospho-tyrosine signaling in mouse models of prostate cancer and human prostate cancer samples. Using quantitative, label-free mass spectrometry, we demonstrated that i) mouse model tumors driven by non-tyrosine kinase oncogenes (eg, AKT) can exhibit elevated tyrosine kinase signaling; and ii) human castration-resistant prostate cancer samples exhibit signatures of druggable tyrosine kinase activity. This work has suggested that prostate cancer patients may benefit from tyrosine kinase inhibitor therapies, despite the lack of mutated or amplified tyrosine kinases in this disease. For these studies, I analyzed samples by mass spectrometry and led the bioinformatic data analysis.
    a. Drake JM, **Graham NA**, Stoyanova T, Sedghi A, Goldstein AS, Cai H, Smith DA, Zhang H, Komisopoulou E, Huang J, Graeber TG, and Witte ON (2012). Oncogene-specific activation of tyrosine kinase networks during prostate cancer progression. *Proceedings of the National Academy of Sciences (USA)*, 109(5), 1643-8. PMCID: PMC3277127
    b. Drake JM, **Graham NA**, Lee JK, Stoyanova T, Faltermeier CM, Sudha S, Titz B, Huang J, Pienta, KJ, Graeber TG and Witte ON (2013). Metastatic castration-resistant prostate cancer reveals intrapatient similarity and interpatient heterogeneity of therapeutic kinases. *Proceedings of the National Academy of Sciences (USA)*, 110(49), E4762-9. PMCID: PMC3856845
    c. Goodwin JF, Kothari V, Drake JM, Zhao S, Dylgjeri E, Dean JL, Schiewer MJ, McNair C, Jones JK, Aytes A, Magee MS, Snook AE, Zhu Z, Den RB, Birbe RC, Gomella LG, **Graham NA**, Vashisht AA, Wohlschlegel JA, Graeber TG, Karnes RJ, Takhar M, Davicioni E, Tomlins SA, Abate-Shen C, Sharifi N, Witte ON, Feng FY, and Knudsen KE (2015). DNA-PKcs mediated transcriptional regulation drives prostate cancer progression and metastasis. *Cancer Cell*, 28(1), 97-113. PMCID: PMC4531387

5. My graduate research focused on the quantitative interplay between intracellular and extracellular signaling pathways. These publications focused on the Wnt/β-catenin pathway, which can be antagonized by extracellular contact (ie, via sequestration of β-catenin at adherens juctions) and promoted via intracellular signaling (ie, non-canonical stabilization of cytoplasmic β-catenin by epidermal growth factor receptor signaling). Because the balance between extracellular and intracellular signaling is often perturbed in cancer (eg, insensitivity to contact inhibition), these studies have contributed a quantitative understanding of how these pathways are deregulated in cancer.
    a. **Graham NA** and Asthagiri AR (2004) "EGF-mediated Tcf/Lef transcriptional activity is essential, but not sufficient, for cell cycle progression in non-transformed mammary epithelial cells," *The Journal of Biological Chemistry*, 279 (22), 23517-24
    b. **Graham NA**, Pope MD, Rimchala T, Huang BK, and Asthagiri AR (2007). A microtiter assay for quantifying protein-protein interactions associated with cell-cell adhesion. *The Journal of Biomolecular Screening*, 12(5), 683-93.
    c. Pope MD, **Graham NA**, Huang BK, and Asthagiri AR (2008). "Automated quantitative analysis of epithelial cell scatter." *Cell Adhesion & Migration*, 2(2), 110-6. PMCID: PMC2634994
    d. Kim JH, Kushiro K, **Graham NA**, Asthagiri AR (2009). Tunable Interplay between epidermal growth factor and cell-cell contact governs the spatial dynamics of epithelial growth. *Proceedings of the National Academy of Sciences (USA)*, 106(27), 11149-53. PMCID: PMC2708686

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40581200/?sort=date&direction=ascending

D. Research Support

Recently Completed Research Support

R25T CA098010 Phelps (PI) 01/2012-12/2014
UCLA Scholars in Oncologic Molecular Imaging program
This project will conduct systems analysis of metabolism in IDH mutant glioblastoma to enable development of PET imaging tracers.
Role: Postdoctoral Fellow

Ongoing Research Support

The Rose Hills Foundation Research Fellowship Graham (PI) 07/01/15-06/30/16
Defining the role of genomic instability in basal-like breast cancer metabolism
This study will investigate the coupled nature of genomic instability (ie, aneuploidy) and aberrant metabolism in models of basal-like breast cancers.
Role: PI

Margaret Early Medical Research Trust Graham (PI) 01/01/16 - 12/31/16
Regulation of Cancer Cell Metabolism by Phosphorylation of Metabolic Proteins
This project will identify phosphorylation sites on metabolic proteins, predict how these phospho-sites regulate metabolic flux in tumor cells, and then validate these functional predictions.
Role: PI

Pending Research Support

None