BIOGRAPHICAL SKETCH

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NAME: Gary L. Johnson, Ph.D.

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

POSITION TITLE: Kenan Distinguished Professor and Chair

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
California State University, Northridge, CA	B.A.	06/1971	Biology
University of Colorado Medical School, Denver, CO	Ph.D.	02/1976	Pharmacology
University of California, San Francisco, CA	Postdoc.	04/1979	Biochemistry

A. Personal Statement

I am the Kenan Distinguished Professor and Chair of the Department of Pharmacology, co-director of the Program in Molecular Therapeutics for the UNC Lineberger Comprehensive Cancer Center, and director of the Human Genome RNAi Screening Facility for automated genome-wide RNAi screens. I have had a research laboratory continuously funded by NIH and NIGMS for more than 35 years. I have served on many NIH committees including the Board of Counselors for the NIDDK, NIGMS Council (*ad hoc*), chaired the NIGMS Pharmacogenetics Review Committee and served on the NIGMS Glue Grant Review Panel. I have served on the scientific advisory boards of two publicly traded biotechnology companies. I have trained 51 postdoctoral fellows and 23 PhD students. Representative past students and fellows currently have positions at Harvard (my first graduate student), Vanderbilt, Oklahoma HSC, Minnesota, Colorado HSC (3 former fellows with faculty positions), North Carolina (in Cell Biology independent of my lab), Loyola and Arizona. Two trainees have successfully started their own companies (one a student, one a fellow). Several have significant leadership roles: one is a Vice President at Bayer Pharmaceutical, one is Associate Director for Research at the Oklahoma Cancer Center, one is chair of Craniofacial Biology, University of Colorado HSC and one is scientific director of the Manitoba Institute for Cell Biology. As a translational basic scientist my research interests focus on understanding the behavior of the kinome *en masse* in human disease. My laboratory has developed chemical proteomics methods that allows measurement of the activation state of ~90% of the kinome that can be applied to cell lines, preclinical animal models, patient-derived xenografts and clinical trials. Relevant to this proposal my laboratory integrates kinome proteomics with next generation sequencing and chromatin epigenetics to define the regulation and dysregulation of the kinome in human diseases - “genoproteomics”.

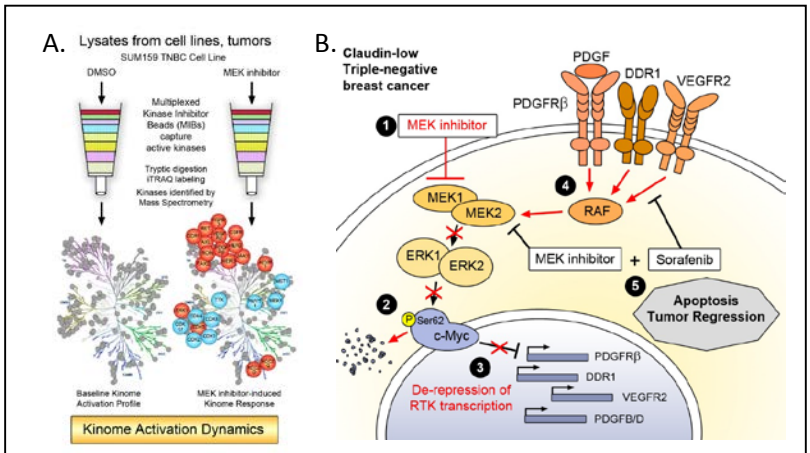

Fig. 1: A) Multiplexed Inhibitor Beads coupled with Mass Spectrometry (MIB/MS) as a technique for whole-kinome activation profiling. B) MEK inhibition induces RTK-based kinome reprogramming in claudin-low triple-negative breast cancer.

1. Duncan, J.S., Whittle, M.C., Nakamura, K., Abell, A.N., Midland, A.A., Zawistowski, J.S., Johnson, N.L., Granger, D.A., Vincent Jordan, N., Darr, D.B., Usary, J., Kuan, P.F., Smalley, D.M., Major, B., He, X., Hoadley, K., Zhou, B. Sharpless, N.E., Perou, C.M., Kim, W.Y., Gomez, S.H., Chen, X., Jin, J., Frye, S.V.,

Earp, H.S., Graves, L.M., **Johnson, G.L.** (2012) Dynamic Reprogramming of the Kinome In Response to Targeted MEK Inhibition In Triple Negative Breast Cancer. *Cell* 149:307-21. PMC3328787
2. Abell, A.N., Jordan, N.V., Huang, W., Prat, A., Midland, A.A., Johnson, N.L., Granger, D.A., Mieczkowski, P.A. Perou C.M., Gomez, S.H., Li, L. and **Johnson, G.L**. (2011) MAP3K4/CBP Regulated H2B Acetylation Controls Epithelial-Mesenchymal Transition in Trophoblast Stem Cells, *Cell Stem Cell*, 8, 525-537. PMC32018823.

B. Positions and Employment

1979-1981 Assist. Prof., Div. of Biology/Med., Sec. of Physiological Chem., Brown Univ., Providence, RI
1981-1988 Assoc. Professor, Dept. of Biochemistry, Univ. of Massachusetts Medical Ctr., Worcester, MA
1988-2000 Senior Scientist, Div. Basic Sciences, National Jewish Health, Denver, CO
1989-2003 Professor, Department of Pharmacology, University of Colorado School of Med., Denver, CO
1989-2003 Member, Cancer Center, University of Colorado School of Medicine, Denver, CO
1994-1999 Director of Cell Biology, Cadus Pharmaceuticals, Inc., Tarrytown, NY/Denver, CO
1996-2000 Director, Program in Molecular Signal Transduction, National Jewish Health, Denver, CO
1999-2003 Associate Director of Basic Sciences, University of Colorado Cancer Center, Denver, CO
1999-2003 Member, Molecular Biology Program, University of Colorado Medical School, Denver, CO
2002-2003 Vice Chair, Department of Pharmacology, University of Colorado Medical School, Denver, CO
2003-present Professor and Chair, Department of Pharmacology, University of North Carolina School of Medicine, Chapel Hill, North Carolina
2003-present Co-director, Program in Molecular Therapeutics, Lineberger Comprehensive Cancer Center, University of North Carolina
2011-present Kenan Distinguished Professor, University of North Carolina School of Medicine, Chapel Hill, North Carolina

Honors

1971 Graduated Magna Cum Laude, 1971 Recipient of National Science Foundation Fellowship, 1976 Recipient of Individual NIH Postdoctoral Fellowship,1980 Established Investigator of the American Heart Association, Chair, 1993 Gordon Research Conference on Second Messengers & Protein Phosphorylation, Keynote Speaker, 1993 Graduate Student Symposium, The University of Kansas, Co-Chair, 1993 American Physiological Society Conference on Signal Transduction and Gene Regulation, Chair, 1995 Gordon Research Conference on Molecular Pharmacology, Keynote Speaker, 1995 Graduate Student Symposium, Emory University, Keynote Speaker, 1995 American Society of Nephrology, Co-Chair, 1996 FASEB Symposium on G Protein Structure & Function, Dean's Distinguished Seminar, 1996 University of Colorado Health Sciences Center, Speaker, International Symposia honoring Edwin G. Krebs, Nagoya, Japan 1996, Merit Award, NIGMS 1998-2008, Co-Chair, 2002 Protein Kinase Keystone Symposium, Plenary Speaker, 2004 Canadian Society of Biochemistry, Molecular and Cell Biology, Keynote Speaker, 2002 Basic Science Lecture: Signal Pathways Activated in Response to Chemotherapeutic Drugs, European Brain Tumor Conference, Copenhagen, Denmark, Co-Chair, 2003 ASCB Meeting, Signal Transduction Determining the Fate of Stem Cells, 2007 ISI Highly Cited Researcher in Biology and Biochemistry (Thomas Scientific, ISIHighlyCited.com), 2007 Beijing Symposium on Cell Signaling: Cancer, Development and Stem Cells, 2008 Johnson-Sokatch Lecture, University of Oklahoma Health Sciences Center, 2008, Directors Distinguished Lectureship, NIEHS, 2011 Seoul National University Symposium on Pharmacological Manipulation of Cancer Cell Proliferation and Transdifferentiation, Plenary Lecture, 2014 FASEB Conference on Protein Phosphorylation, Cellular Plasticity and Signaling Rewiring, Keynote Speaker

C. Contribution to Science

1. My research laboratory was one of 2-3 laboratories in the early 90's that demonstrated oncogenes including Ras and Src as well as specific GPCRs activated the MAPK, ERK1/2. We also cloned a series of MAP3Ks (MEKK1, 2, 3 & 4) and showed they differentially regulated ERK1/2, JNK and p38. This was groundbreaking because it defined the MAPK signaling network as a large network of MAP3Ks, MAP2Ks and MAPKs and not a series of linear pathways. We went on to define the role of MAPKs in proliferation, apoptosis, migration and invasion. Both gene knockouts and knockins were used to define MAP3K function in mice. My laboratory has published approximately 250 papers related to the function of MAPK networks in different aspects of human disease.

a. Gallego, C., Gupta, S.K., Heasley, L.E., Qian, N.-X. and **Johnson, G.L.** (1992) Mitogen-activated protein kinase activation resulting from selective oncogene expression in NIH 3T3 and Rat 1a cells. *Proc Natl Acad Sci USA* 89, 7355-7359 PMC50199

b. Lange-Carter, C.A., Pleiman, C.M., Gardner, A.M., Blumer, K.S. and **Johnson, G.L.** (1993) A divergence in the MAP kinase regulatory network defined by MEK kinase and Raf. *Science* 260, 315-319. PMID: 8385802

c. Minden, A., Lin, A., McMahon, M., Lange-Carter, C., Dérijard, B., Davis, R.J., **Johnson, G.L.** and Karin, M. (1994) Differential activation of ERK and JNK mitogen-activated protein kinases by Raf-1 and MEKK. *Science* 266, 1719-1723. PMID: 7992057
d. Yujiri, T., Sather, S., Fanger, G.R. and **Johnson, G.L.** (1998) Role of MEKK1 in cell survival and activation of JNK and ERK pathways defined by targeted gene disruption. *Science* 282, 1911-1914. PMID: 9836645

2. Different agonists do not necessarily activate receptors through stabilization of the same active state. We discovered and I believe the first lab to publish that different agonists targeting the same GPCR have a "bias" and do not activate signaling pathways with the same intensity. We termed this "biased agonism" and "asymmetric signaling" in our studies with the bombesin receptor in small cell lung carcinoma. Biased agonism is now a major emphasis for guiding structure-activity relationships and the development of new drugs in the pharmaceutical industry.
a. Heasley, L.E., Zamarripa, J., Storey, B., Helfrich, B., Mitchell, F.M., Bunn, Jr., P.A. and **Johnson, G.L.** (1996) Discordant signal transduction and growth inhibition of small cell lung carcinomas induced by expression of GTPase-deficient $G\alpha_{16}$. *J Biol Chem* 271, 349-354 PMID: 8550585
b. Jarpe, M., Gerwins, P., Buhl, A.M., Mitchell, F. and **Johnson, G.L.** (1998) [D-Arg^{1}, D-Phe^{5}, D-Trp^{7,9}, Leu^{11}] Substance P acts as a biased agonist toward neuropeptide and chemokine receptors. *J Biol Chem* 273, 3097-3104. PMID: 9446627

3. We cloned a scaffold protein that organized a signaling complex of Rac1-MEKK3-MKK3 and p38 now known as cerebral cavernous malformation protein 2 (CCM2). We showed that CCM2 can be in a physical complex with two other scaffold proteins: CCM1 and CCM3. The CCM complex regulates Smurf1, an E3 ligase that targets RhoA and specific Smads for degradation. Inhibition of Rho kinase causes a significant but partial rescue of the CCM phenotype and this treatment is going into clinical trials for CCM. This continues to be an active area of research in my lab. We have created an iPS library of cells from patients having mutations in the *ccm*1, 2 or 3 genes. We differentiate these cells to endothelial cells (ECs) to study the phenotype of human ECs harboring *ccm* gene mutations. We have also shown that CCM1, 2 and 3 differentially regulate transcription of genes controlling cell adhesion and endothelial mesenchymal transition. Our current studies show that CCM3 is an overlapping but distinct disease from CCM1 and 2.
a. Uhlik, M.T., Abell, A.N., Johnson, N.L., Sun W., Cuevas, B.D., Lobel-Rice,K.E., Horne, E.A., Dell'Acqua, M.L. and **Johnson, G.L.** (2003) Rac-MEKK3-MKK3 Scaffolding for p38 MAPK Activation During Hyperosmotic Shock. *Nat Cell Biol* 5, 1104-1110. PMID: 14634666
b. Hilder, T.L., Malone, M.H., Bencharit, S. Colicelli, J., Haystead, T.A. **Johnson, G.L.** and Wu, C.C. (2007) Proteomic identification of the cerebral cavernous malformation signaling complex. *J Proteome Res,* 6:4343-4355. PMID: 17900104
c. Crose, L.E., Hilder, T.L., Sciaky, N., **Johnson G. L.** (2009) Cerebral cavernous malformation 2 protein promotes Smad ubiquitin regulatory factor 1-mediated RhoA degradation in endothelial cells. *J Biol Chem* 284:13301-13305 PMC2679429
d. Borikova, A.L., Dibble, C.F., Sciaky, N., Welch, C.M., Abell, A.N., Bencharit, S. and **Johnson, G.L**., (2010) Rho kinase inhibition rescues the endothelial cell cerebral cavernous malformation phenotype. (cover) *J Biol Chem* 285:11760-11764 PMC2852911

4. The *Cell Stem Cell* paper we published (see Abell et al in personal statement) defined for the first time a mutation that captured a self-renewing tissue stem cell in a permanent state of EMT. This is one of several papers we published on function of the MAP3K, MEKK4, in controlling EMT. Our work was the first to show that MEKK4-JNK controlled the histone acetyltransferase, CBP, for histone acetylation regulating EMT. From these studies we used high-throughput microscopy screens to define the function of the SWI/SNF chromatin modifying complex in EMT. Similar screening methods defined specific microRNAs in synthetic lethality screens involving inhibition of the MEK-ERK1/2 pathway and the Tousled-like kinases in regulating herpes virus latency.
a. Vincent Jordan, N., Prat, A., Abell, A.N., Zawistowski, J.S., Sciaky, N., Karginova, O.A., Zhou., B, Golitz, B.T., Perou, C.M., **Johnson, G.L**.. (2013) SWI/SNF Chromatin-remodeling Factor Smarcd3/Baf60c Controls EMT by Inducing Wnt5a Signaling. *Mol Cell Biol* 33, 3011-3025. PMC3719671
b. Zawistowski, J.S., Nakamura, K., Parker, J.S., Granger, D.A., Golitz, B.T., **Johnson, G.L.** (2013) miR-9-3p targets integrin beta 1 to sensitize claudin-low breast cancer cells to MEK inhibition. *Mol Cell Biol* 33: 2260-74. PMC3648081
c. Dillon, P.J., Gregory, S.M., Tamburro, K., Sanders, M.K., **Johnson, G.L**., Raab-Traub, N., Dittmer, D.P., Damania, B. (2013) Tousled-like kinases modulate reactivation of gamma herpes viruses from latency. *Cell Host Microbe* 13, 204-214. PMC360241

d. Abell, A.N. and **Johnson, G.L.** (2014) Implications of Mesenchymal Cells in Cancer Stem Cell Populations: Relevance to EMT *Curr Pathobiol Rep.* 2, 21–26. PMC4266994

5. The Duncan et al *Cell* paper (see personal statement) describes the development of multiplexed inhibitor beads coupled with mass spectrometry to define kinase activation dynamics at a kinome-wide scale. Our methods are capable of measuring the activation and inhibition of the kinome *en masse* with the ability of capturing approximately 90% of the kinome. We have used our methods to define the adaptive bypass mechanisms that result in the lack of durable responses to targeted kinase inhibitors in the clinic. We published a paper in *Cell Reports* that showed how BET-bromodomain inhibitors could block the transcriptional upregulation of receptor tyrosine kinases making the response to kinase inhibition durable. We are involved in multiple clinical trials using these methods.
a. Graves, L.M., Duncan, J.S., Whittle, M.C., **Johnson, G.L.** (2013) The dynamic nature of the kinome. *Biochem J*. 450, 1-8. PMC3808244
b. **Johnson, G.L.**, Stuhlmiller, T.J., Angus, S.P., Zawistowski, J.S., Graves, L.M. (2014) Molecular Pathways: Adaptive Kinome Reprogramming in Response to Targeted Inhibition of the BRAF-MEK-ERK Pathway in Cancer. *Clin Cancer Res.* 20: 2516-2522 PMC4024346
c. Stuhlmiller, T.J., Earp, H.S., **Johnson, G.L.** (2014) Adaptive Reprogramming of the Breast Cancer Kinome. *Clin Pharmacol Ther*. 2014 Jan 10. doi: 10.1038/clpt.2014.8. PMC4091669
d. Stuhlmiller, T.J., Miller, S.M., Zawistowski, Kazuhiro Nakamura, K., Beltran, A., Duncan, J.S., Collins, K.L.A., Granger, D.A., Rachel A. Reuther, R.A., Graves, L.M., Gomez, S.M., Kuan, P-F., Joel S. Parker, J.S., Chen, X., Sciaky, N., Carey, L.A., Shelton Earp, H.S., Jin, J., **Johnson, G.L.** (2015) Inhibition of Lapatinib-induced Kinome Reprogramming in ERBB2-positive Breast Cancer by Targeting BET Family Bromodomains, *Cell Reports* PMC4408261

Complete List of Published Work:
http://www.ncbi.nlm.nih.gov/sites/myncbi/gary.johnson.1/bibliography/40433719/public/?sort=date&direction=ascending.

D. Research Support
Ongoing Research Support

R01 GM101141 (Johnson) 04/15/2012–03/31/2016
NIH/NCI
Kinome Reprogramming in Response to Targeted Kinase Inhibitors
Rationally devising novel kinase inhibitor combination therapies requires detailed knowledge of kinome activity. MIB/MS technology is used to assess global kinome behavior and its response to small molecule inhibitors leading to new and effective combination therapies to treat disease.

R01 GM068820 (Johnson) 08/01/2003 - 07/31/2016
NIH/NIGMS
Function of Cerebral Cavernous Malformation Proteins
The key aspects of this proposal are to define the cellular regulatory functions of CCM proteins, the changes in CCM-regulated signaling networks in resected patient lesions, and to develop innovative models of CCM using patient-specific induced pluripotent stem cells (hiPSCs).

R01 GM068820-09S1 (Johnson) 08/01/2003 - 07/31/2016
NIH/NIGMS -
Function of Cerebral Cavernous Malformation Proteins (Administrative Supplement)
Administrative supplement in support of goals/aims of prime

IIRI2225201 (Johnson, Earp) 04/13/13 – 03/31/17
SG Komen Breast Cancer Foundation
Whole Kinome Profiling and Remodeling in HER2+ Breast Cancer
This project seeks to understand the biology of HER2+ breast cancer and the response of HER2+ breast cancer to HER2-targeted agents in order to identify and prioritize combination regimens most likely to be effective in circumventing resistance.

P50 CA058223 (Earp) 08/05/1997 - 08/31/2017
NCI (Johnson Project 4)

SPORE in Breast Cancer
Defining Kinome Activity for Novel Therapies in Triple Negative Breast Cancer
Project 4 of the Breast SPORE is defining the regulation of the kinome activation state in TNBC in response to targeted inhibitors. It includes a window trial where TNBC tumors from patients treated with Trametinib for one week are analyzed for reprogramming of their kinome.

N/A (Damania) 12/01/2013-11/30/2015
Leukemia and Lymphoma Society (LLS)
Novel Technology for Targeting and Understanding NHL Biology
This project proposes to profile the activation state of the kinome of different B-NHL sub-types to stratify B-NHL according to their baseline kinome signature and reprogramming response to clinically relevant therapies.

N/A (Mosse) 07/01/2014-06/30/2019
The Children's Hospital of Philadelphia Research Institute Subcontract
Targeting Oncogenic ALK Signaling in Neuroblastoma
Multiplexed inhibitor beads coupled with mass spectrometry is used to define the activation state of the expressed kinome in neuroblastoma. We are studying changes in the kinome that are induced by expression of activating ALK mutations. The goal is to find kinases that are activated in ALK driven neuroblastoma that could be used as novel therapeutic targets to treat children.

U01 MH104999 (Johnson) 07/01/2014-06/30/2017
NIH
Activation and Regulation of the Understudied Kinome Using MIB/MS Technology
We use Multiplexed Inhibitor Beads (MIBs), mixtures of covalently immobilized, linker adapted kinase inhibitors coupled with mass spectrometry (MS), to assess the activation state of the kinome en masse to identify understudied kinases within the druggable genome that warrant new chemical probe development..

N/A (Major) 12/01/2014-11/30/2017
V Foundation for Cancer Research $181,818
Team Science Approach for defining the activation state and dynamic reprogramming of the kinome in aerodigestive cancer
In this proposal MIB/MS and quantitative mass spectrometry will be used to study the kinome activation state of aerodigestive tumors from cancer patients before and after therapy.

Completed Research (last 3 years)
W81XWH-12-1-0129 (Ellis, Johnson) 09/30/2012–09/29/2014
CDMRP
Targeted therapy for MAP3K1 and MAP2K4 Mutant Estrogen Receptor Positive Breast Cancer
The work in this proposal attempts to identify protein kinases that could be targeted for inhibition to make new more effective combination therapies to treat breast cancer.