BIOGRAPHICAL SKETCH

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NAME: **Gary L. Johnson**

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

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
California State University, Northridge, CA	BA	06/1971	Biology
University of Colorado Medical School, Denver, CO	PhD	02/1976	Pharmacology
University of California, San Francisco, CA	Postdoc	04/1979	Biochemistry

A. Personal Statement

My academic position at UNC is Professor in the Department of Pharmacology where I served as chair of the department for 14 years from 2003-2017. I was also the Kenan Distinguished Professor from 2011-2019. I currently continue as co-director of the Program in Molecular Therapeutics for the Lineberger Comprehensive Cancer Center and director of the Human Genome RNAi/CRISPR Screening Facility. I have had a research laboratory continuously funded by NIH for 40 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 53 postdoctoral fellows and 27 PhD students. Representative past students and fellows currently have positions at Harvard, Vanderbilt SOM, Oklahoma HSC, Minnesota HSC, Emory SOM, Colorado HSC, North Carolina SOM (in Cell Biology independent of my lab), Fox Chase Cancer Center, Indiana SOM and Arizona SOP. Two trainees have successfully started their own companies (one a student, one a fellow). Several have significant leadership roles including: Vice President at Bayer Pharmaceutical, Associate Director for Research at the Oklahoma Cancer Center, chair of Craniofacial Biology, University of Colorado HSC, chair of pediatric Oncology at Emory, and scientific director of the Manitoba Institute for Cell Biology. Thus, I have extensive experience successfully mentoring post-doctoral fellows and students, directing a large basic science department and evaluating innovative scientific initiatives. As a translational basic scientist my research interests focus on understanding the behavior of the kinome en masse in cancer. My laboratory has developed chemical proteomics methods that allows measurement of the functional state of ~90% of the kinome that can be applied to cell lines, preclinical animal models, patient-derived xenografts and clinical trials. My laboratory integrates kinome proteomics with next generation sequencing and chromatin epigenetics to define the dynamic behavior of the kinome at both baseline and with perturbation in preclinical cancer models and patient trials. h-index: 105; Citations: 49,204 (July, 2020)

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. 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

3. Zawistowski, J.S., Bevill, S.M., Goulet, D.R., Stuhlmiller, T,J., Beltran, A.S., Olivares-Quintero, J.F., Singh, D., Sciaky, N., Parker, J.S., Rashid, N.U., Chen, X., Duncan, J.S, Whittle, M.C., Angus, S.P., Velarde, S.H., Golitz, B.T., He, X., Santos, C., Darr, D.B., Gallgher, K., Graves, L.M., Perou, C.M., Carey, L.A., Earp H.S., Johnson, G.L. (2017) Enhancer Remodeling During Adaptive Bypass to MEK Inhibition Is Attenuated by Pharmacological Targeting of the P-TEFb Complex. Cancer Discovery 7:302-321. PMID: 28108460
4. Wong, J.P., Stuhlmiller, T.J., Giffin, L.C., Lin, C., Bigi, R., Zhao, J., Zhang, W., Bravo Cruz, A.G., Park, S.I., Earp, H.S., Dittmer, D.P., Frye, S.V., Wang, X., Johnson, G.L., Damania, B. (2019) Kinome profiling of non-Hodgkin lymphoma identifies Tyro3 as a therapeutic target in primary effusion lymphoma. Proc Natl Acad Sci U S A. 2019 Jul 25. doi: 10.1073/pnas.1903991116. [Epub ahead of print] PMID: 31346082

B. Positions and Honors

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
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
2003-2016	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
2011-2019	Kenan Distinguished Professor, Department of Pharmacology, University of North Carolina School of Medicine, Chapel Hill, North Carolina

Other Experience and Professional Memberships

1994-1999	Director of Cell Biology, Cadus Pharmaceuticals, Inc., Tarrytown, NY/Denver, CO
2001-2005	Consultant, Atherogenics, Inc., Alpharetta, GA
2014-2017	Co-founder, KinoDyn, Inc., Durham, NC
2003-present	American Society of Pharmacology and Experimental Therapeutics (ASPET)
2014-present	American Association for Cancer Research (AACR)

Honors/Keynote Presentations

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
1993	Chair, Gordon Research Conference on Second Messengers & Protein Phosphorylation,
1993	Keynote Speaker, Graduate Student Symposium, The University of Kansas
1993	Co-Chair, American Physiological Society Conference on Signal Transduction and Gene Regulation
1995	Chair, Gordon Research Conference on Molecular Pharmacology
1995	Keynote Speaker, Graduate Student Symposium, Emory University
1995	Keynote Speaker, American Society of Nephrology
1996	Co-Chair, FASEB Symposium on G Protein Structure & Function
1996	Dean's Distinguished Seminar, University of Colorado Health Sciences Center
1996	Speaker, International Symposia honoring Edwin G. Krebs, Nagoya, Japan
1998	2008 Merit Award, NIGMS
2002	Co-Chair, Protein Kinases Keystone Symposium

2004 Plenary Speaker, Canadian Society of Biochemistry, Molecular and Cell Biology
2002 Keynote Speaker, Basic Science Lecture: Signal Pathways Activated in Response to Chemotherapeutic Drugs, European Brain Tumor Conference, Copenhagen, Denmark
2003 Co-Chair, ASCB Meeting, Signal Transduction Determining the Fate of Stem Cells
2007 ISI Highly Cited Researcher in Biology and Biochemistry (Thomas Scientific, ISIHighlyCited.com)
2007 Keynote Speaker, 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 Plenary Lecture, Seoul National University Symposium on Pharmacological Manipulation of Cancer Cell Proliferation & Transdifferentiation
2012 Meet the Professor Lecture, AACR Annual Meeting
2014 Keynote Speaker, FASEB Conference on Protein Phosphorylation, Cellular Plasticity & Signaling Rewiring
2016 Keynote Speaker, Gordon Conference on G Protein Coupled Receptors & Protein Phosphorylation
2018 Hyman L. Battle Distinguished Cancer Research Award

C. Contributions 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□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-Arg1, D-Phe5, D-Trp7,9, Leu11] 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 ccm1, 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. Mobley, R.J., Raghu, D., Duke, L.D., Abell-Hart, K., Zawistowski, J.S., Lutz, K., Gomez, S.M., Roy, S., Homayouni, R., Johnson, G.L., Abell, A.N. (2017) MAP3K4 Controls the Chromatin Modifier HDAC6 during Trophoblast Stem Cell Epithelial-to-Mesenchymal Transition. Cell Reports. 2017 18: 2387-2400. PMID: 28273454

5. 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. Blocking adaptive bypass resistance to kinase inhibitors at its epigenetic root has significant clinical implications for making therapeutic responses more durable. The relevance of such an approach is evident in our TNBC studies. The adaptive response signatures in BL versus CL cell lines and patient tumors are different but the two subtypes are treated similarly in the clinic. If the adaptive response to single kinase inhibitors such as trametinib could be blocked epigenetically, by targeting enhancer formation/remodeling by inhibiting P-TEFb constituents such as BRD4, p300, JMJD6, CDK7 or CDK9 adaptive resistance could be prevented and possibly reversed.

a. 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
b. 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
c. Angus, S.P., Zawistowski, J.S., Johnson, G.L. (2017) Epigenetic Mechanisms Regulating Adaptive Responses to Targeted Kinase Inhibitors in Cancer. Ann. Rev. Pharmacol. Tox. 58:209-229. PMID: 28934561

Complete List of Published Work:

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