BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Klaus Michael Hahn	Professor of Pharmacology
eRA COMMONS USER NAME (credential, e.g., agency login)	
KLAUS_HAHN	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Pennsylvania	BA	1981	Biochemistry, Philosophy
University of Virginia	Ph.D.	1986	Chemistry
Carnegie Mellon University	Postdoctoral	1987-1991	Chemistry, Cell Biology
The Scripps Research Institute	Sr. Rsch. Assoc.	1992-1994	Immunology

Personal Statement

Our lab focuses on two synergistic areas: development of novel tools to visualize and manipulate protein activity in living cells and animals, and application of these tools to address questions re the spatiotemporal dynamics of signaling *in vivo*. Our biological studies center on cytoskeletal and adhesion dynamics, their role in signaling crosstalk, and immune cell function. We are currently studying cell protrusion/retraction mechanisms, the role of cytoskeletal dynamics in signaling crosstalk, the morphodynamics of macrophages, and platelet function. With collaborators, we are extending our cell biology studies to examine metastasis and immune cell function in 3D models.

While addressing specific molecules for our biological studies, we produce generally applicable new approaches to visualize and control signaling. These include fluorescent biosensors to quantify conformational changes of endogenous proteins, visualizing and controlling multiple protein activities in the same cell, and novel biosensor designs that reduce perturbation of normal biology. We have developed biosensors based on engineered protein scaffolds to access otherwise inaccesible molecules, and synthesized novel fluorescent dyes that enhance sensitivity, enable multiplexing and lead to biosensors for single molecule microscopy. We are devising new approaches to activate or inactivate proteins with seconds and submicron resolution *in vivo*, using engineered domains that respond to light or small molecules. In technique development, we are currently focused on Rho family GTPase and Src kinase signaling networks.

This work greatly benefits from interactions with collaborators who focus on computational image analysis, modeling of signaling dynamics, and developing novel microscopes.

Positions and Employment

1994-1997 Assistant Professor, Department of Neuropharmacology, Scripps Research Institute
1997-2000 Assistant Professor, Department of Cell Biology, Scripps Research Institute
2000-2004 Associate Professor, Department of Cell Biology, Scripps Research Institute
2004-present Thurman Distinguished Professor of Pharmacology, University of North Carolina, Chapel Hill
2004-present Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill
2006-present Carolina Cardiovascular Biology Center, University of North Carolina, Chapel Hill
2007-present Department of Medicinal Chemistry, University of North Carolina
2009-present UNC Center for Computational and Systems Biology
2009-present Founder and Director, UNC-Olympus Imaging Center

Honors

1984 Dupont graduate fellowship
1988 Muscular Dystrophy Association postdoctoral fellowship
1998 National Institutes of Health James A. Shannon Directors Award
2004 Ronald Thurman Distinguished Professor of Pharmacology

2009 NIH Roadmap Transformative R01 Award
2010 Fellow of the American Association for the Advancement of Science
2010 Nature Reviews - Molecular Cell Biology: "10 breakthroughs of the decade"

Plenary and Keynote lectures: Annual Meeting of the Japanese Biochemical Society, 2003; International Society for Analytical Cytology, 2006; NIH Conference on Imaging Probes, 2007; International Conference of Systems Biology, 2009; Korean Society for Biochemistry and Molecular Biology, 2010; Twelfth International Conference on Methods and Applications of Fluorescence 2011; Leica Scientific Forum France, 2012; Snyder Institute, U. Calgary Endowed Chair lecture, 2013; Labex France Signalife, 2014; SPIE Photonics West, 2015.

Other Professional Activities

Editorial board, Biophysical Journal, 2013-present

Study sections and grant review: NIH Biophysics study section *ad hoc* reviewer, 2001; The Research Corporation, 2002; Argonne National Laboratories, 2002; Ecole Polytechnique Federale De Lausanne, 2002; NIH study section: Cellular and molecular imaging methods, 2003; NIH Roadmap study section: Molecular Libraries and High Throughput Screening, 2006; Roadmap initiative formulation—Nanomedicine program, 2006; Roadmap initiative oversight—State of Science: molecular imaging and libraries at NIH, 2006; The Wellcome Trust, England, 2006-present; Italian Association for Cancer Research, 2006-present; NIH Microscopic Imaging study section *ad hoc* reviewer, 2007; NIH Cellular Structure and Function study section *ad hoc* reviewer, 2008; NCI Innovative Molecular Technologies Program, ad hoc reviewer, 2009; NIGMS Special emphasis panel on cellular imaging, 2009; Bioengineering special emphasis panel, 2009; ARRA Challenge grants study section, 2009; ARRA Go grants study section 2009; NIH College of CSR reviewers 2010-2012. NIH Enabling Biophysical and Imaging Technologies ad hoc reviewer 2011. Director's New Innovator Awards study section, 2012; Enabling bioanalytical and imaging technologies (EBIT) study section, ad hoc panel, 2012 (chair); NCI Provocative questions review panel, 2012; NIH EBIT study section 2014; NIH Division of Intramural Research, site visit 2014.

Organization of scientific meetings: Organizer, Signal Transduction Targets for Effective Therapeutics, Cambridge Healthtech Institute, 2004; Organizer, Molecular Microscopy of Living Cells, ASCB Annual meeting, 2004; Program Committee, International Society for Analytical Cytology Annual Meeting, 2007; Organizer, ASCB subgroup meeting on High Performance Image Analysis and Photomanipulative Techniques for Cell Biology, 2007; Co-chair, Imaging and Biosensors, ASCB annual meeting, 2008; Session chair, Biophysical Society Meeting, 2011; ASCB annual conference program committee, 2011; Co-organizer, Keystone meeting on Optogenetics, 2015.

Consulting and advisory boards: Scientific Advisory Board, Q3DM Company, 2001-2003; Consultant, Amersham Corporation, 2002; Scientific Advisory Board, Panomics Company, 2003-2008; Sigma Chemical Company biosensor advisory board, 2006-2008; Scientific Advisory Board, NIH Center for Computer Integrated Systems in Microscopy and Manipulation, 2011-present; UNC Translational and Clinical Sciences Institute, 2013-present.

Professional memberships: American Society for Cell Biology; American Chemical Society; Biophysical Society; International Society for Analytical Cytology; American Association for the Advancement of Science; The Protein Society.

Patents

US 6,951,947 (2005); US 7,176,037 (2007); US 7,351,797 (2008); US 7,592,188 (2009); US 8,835,632 (2014); 8,859,232 (2014); PCT/US2015/010269 (2014); On dye chemistry, biosensors, protein photomanipulation, and engineered allosteric activation.

Peer-reviewed publications (15 from >100)

Kraynov, V.S., Chamberlain, C.E., Bokoch, G.M., Schwartz, M.A., Slabaugh, S., and Hahn, K.M. Localized Rac Activation Dynamics Visualized in Living Cells. *Science* 290:333-337, 2000.

Toutchkine, A., Kraynov, V., and Hahn, K.M. Solvent-Sensitive Dyes to Report Protein Conformational Changes in Living Cells, *J. Amer. Chem. Soc***.** 125:4132-4145, 2003.

Nalbant, P., Hodgson, L., Kraynov, V., Toutchkine, A., and Hahn, K.M. Activation of Endogenous Cdc42 Visualized in Living Cells. *Science* 305:1615-1619, 2004.

Subauste, M., Pertz, O., Adamson, E., Turner, C.E., Junger, S., and Hahn, K.M. Vinculin modulation of Paxillin-FAK interactions regulates ERK to control survival and motility. *J. Cell Biol.* 165:171-181, 2004. PMC2172187.

Pertz, O., Hodgson, L., Klemke, R., and Hahn, K.M. Spatio-temporal dynamics of RhoA activity in migrating cells. *Nature* 440:1069-1072, 2006.

Birkenfeld, J., Nalbant, P., Bohl, B.P., Pertz, O.P., Hahn, K.M., and Bokoch, G.M. GEF-H1 modulates localized RhoA activation during cytokinesis under the control of mitotic kinases. *Developmental Cell* 12:699-712, 2007. PMC1965589.

Machacek, M., Hodgson, L., Welch, C., Elliot, H., Pertz, O., Nalbant, P., Abell, A., Johnson, G., Hahn, K.M.* and Danuser, G.* Coordination of Rho GTPase activities during cell protrusion. *Nature* 461:99-103, 2009. PMC2885353.

Wu, Y, Frey, D., Lungu, O. I., Jaehrig, A., Schlichting, I., Kuhlman, B. and Hahn, K.M. Genetically-encoded photoactivatable Rac reveals spatiotemporal coordination of Rac and Rho during cell motility. *Nature* 461:104-110, 2009. PMC2766670.

Yoo, S.K., Deng, Q., Cavnar, P. J., Wu, Y.I., Hahn, K.M., Huttenlocher, A. Differential Regulation of Protrusion and Polarity by PI(3)K during Neutrophil Motility in Live Zebrafish. *Developmental Cell* 18(2): 226-236, 2010. PMC2824622.

Wang, X., He, L., Wu, Y.I., Hahn, K.M., and Montell, D.J. Light-mediated activation reveals a key role for Rac in collective guidance of cell movement in vivo. *Nature Cell Biol.* 12(6): 591-7, 2010. PMC2861620.

Karginov, A.V., Ding, F., Kota, P., Dokholyan, N.V., and Hahn, K.M. Engineered allosteric activation of kinases in living cells. *Nature Biotech.* 28(7): 743-7, 2010. PMC2902629.

Karginov, A. V., Zou, Y., Shirvanyants, D., Kota, P., Dokholyan, N. V., Young, D. D., Hahn, K. M.*, and Deiters, A.* Light Regulation of Protein Dimerization and Kinase Activity in Living Cells Using Photocaged Rapamycin and Engineered FKBP. *J. Am. Chem. Soc.* 133(3): 420-423, 2011. PMC3133816

Gulyani, A., Vitriol, E., Allen, R., Wu, J., Gremyachinskiy, D., Lewis, S., Dewar, B., Graves, L., Kay, B., Elston, T., and Hahn, K.M. A biosensor generated via high-throughput screening quantifies cell edge Src dynamics. *Nature Chem Bio.* 7:437-444, 2011. PMC3135387

Karginov, A., Tsygankov, D., Berginski, M., Chu, P-H., Trudeau, E., Yi, J.J., Gomez, Shawn, Elston, T.C. and Hahn, K.M. Dissecting motility signaling through activation of specific Src-effector complexes. *Nature Chem. Bio.* 10(4):286-90, 2014. PMC4064790

Chu, P-H., Tsygankov, D., Berginski, M.E., Dagliyan, O., Gomez, S.M., Elston, T.C., Karginov, A.V., and Hahn, K.M. Engineered kinase activation reveals unique morphodynamic phenotypes and associated trafficking for Src family isoforms. *Proc. Natl. Acad. Sci. U.S.A.* 111(34):12420–12425, 2014. PMC4151743

<u>Research Support</u> *(selected ongoing and past 3 years)*

R01 CA175747 (Der, Hahn) 12/2013 – 11/30/2018 Role: PI
NIH
<u>Mechanisms of PAK1 activation, signaling and tumor resistance</u>
In this project we will develop and apply three state-of-the art technologies to dissect the spatio-temporal regulation of PAK1 signaling and its consequences: a PAK1 biosensor, an inducible PAK1, and kinome-wide profiling. Our studies will build on two emerging concepts in signal transduction, to define the critical role of spatial regulation in defining PAK1 substrate utilization and biological output, and to profile the dynamic reprogramming of the kinome in response to PAK1 inhibition, leading to mechanisms of PDAC de novo and acquired resistance to pharmacologic PAK1 inhibition.

N/A (Hahn, Huttenlocher) 07/01/2012 – 06/30/2017 Role: PI
University of Wisconsin (NIH)
<u>A toolkit for imaging and photo-manipulation of signaling in zebrafish</u>
The long term goal of the proposed research is to make the visualization and manipulation of signaling practical in zebrafish, thereby enabling broad application to areas of developmental biology and disease pathogenesis.

R01 HL114388 (Hahn, Doerschuck, Burridge) 04/01/2012 – 06/30/2017 Role: PI
NIH
Rho-mediated Signaling in Lung Endothelial Cells Induced by Neutrophil Adhesion
The proposed studies address signaling pathways that regulate neutrophil passage across the endothelium during inflammation and will contribute to an integrated model of endothelial adhesion molecule signaling, incorporating spatial and temporal control that is novel and important to a comprehensive understanding of inflammation.

P01 GM103723 (Hahn, Burridge, Danuser, Hall, Sondek) 12/01/2012 – 11/30/2017 Role: Pgm Proj leader
NIH
Spatio-temporal dynamics of GEF-GTPase networks
This PPG will bring together multiple investigators to examine the circuitry of GEF-GTPase interactions in real time. We will develop new methodology for visualization, photomanipulation, and image analysis of these circuits *in vivo*, and will explore their role in motility, polarization, mechanotransduction and tissue migration.

R01 (Hahn, Kuhlman, Stahl) 10/2013 - 9/2017 Role: PI
NIH
Spatiotemporal Control of the Epigenome via Photoactivatable Nuclear Localization
The aim of this proposal is to create a general approach for the control of epigenetic modifications that is reversible and can be applied at specific times in development to a specified set of cells.

1 U01GM094663-01 (Liddington) 09/30/2010–06/30/2015 Role: Project leader
NIH
Assembly, dynamics and evolution of cell-cell and cell-matrix adhesions
The investigators work with the NIH Protein Structure Initiative (PSI) to determine the structures of adhesion proteins and apply that knowledge in a range of experimental approaches to understand adhesion signaling. Hahn lab is generating biosensors and caged proteins for adhesion signaling.

Transformational Roadmap Award (Hahn, Danuser) 10/2009-09/2014 Role: PI
NIH
Quantitative imaging of signaling networks
We are developing complementary biosensor designs and image processing approaches to enable high resolution mapping of signaling networks in vivo.

RGP0022/2010-C102 (Hahn, Kasai, Kuhlman) 08/01/2010-07/31/2014 Role: PI
Human Frontiers in Science Program
Optogenetics for small G-proteins and protein kinases in neuroscience
This grant focuses on producing new tools to turn proteins on and off with light in neuronal spines. Specific targeting strategies and photoactivatable proteins are being developed for neurodevelopmental studies.

N/A (Bergmeier, Campbell, Hahn) 01/01/2013 – 12/31/2014 Role: PI
NC Biotechnology Center
Multidisciplinary approach to study the CalDAG-GEFI/Rap1 signaling module in platelets
The goals of this proposal are to characterize the molecular mechanism(s) by which the C1-like domain contributes to CalDAG-GEFI function, to generate unique tools for mechanistic studies on the CalDAG-GEFI/Rap1 signaling module, and to test new findings in preclinical models of thrombotic disease.