

BIOGRAPHICAL SKETCH

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NAME: Klaus Michael Hahn

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POSITION TITLE: Professor of Pharmacology

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
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: developing molecular tools to visualize and control signaling in living cells, and asking how the spatio-temporal dynamics of protein activity govern signaling circuits. Our biological studies center on clinically important cell behaviors -- phagocytosis, platelet production, adhesion signaling and immune cell interactions. We try to uncover basic signaling principles using these cells as models of chemical-mechanical interactions in signaling networks. We have begun studies of immune and cancer cell migration in the cancer microenvironment.

Our molecular imaging tools are focused on specific molecules for our biological studies, but we aim to produce broadly applicable approaches that others can use to visualize and control protein behavior. These include new biosensor designs that minimally perturb signaling, enabling us to examine low abundance proteins and to visualize multiple proteins simultaneously. We are developing means to control endogenous proteins with light, and engineering allosteric networks in proteins to confer control by light or small molecules. By precisely producing and visualizing localized signaling transients, we ask quantitative questions about signaling dynamics in cell decision making.

We are grateful to be working closely with other laboratories who model signaling dynamics, develop novel microscopes and quantify complex behavior in microscope images.

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
 2009-2017 Founder and Director, UNC-Olympus Imaging Center
 2009-present UNC Center for Computational and Systems Biology
 2015-present Co-Director, NIH P41 Center: Computer Integrated Systems for Microscopy and Manipulation

Honors

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; Future of Imaging Symposium, U. Calgary 2015, ABRF national meeting 2016.

Other Professional Activities

Editorial board, Biophysical Journal, 2013-2016

Standing member, NIH Cellular and Molecular Technologies study section, 2015-present

NCI Frederick National Laboratory Advisory Committee, 2016-present

Other 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; NIH EBIT study section standing member 2015-present.

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.

Contributions to Science

Biosensors. I have focused for my whole career on developing and applying fluorescent biosensors. Our work has demonstrated the value of biosensors, provided approaches applicable to many proteins, and encouraged what is now a widely used technique. My laboratory has developed biosensors for GTPases, GEFs, kinases and GTPase effectors. We have used designs based on intermolecular and intramolecular FRET, environment sensing dyes, and 'affinity reagents' that report the conformational states of endogenous proteins. We continue to focus on new approaches to extend biosensor imaging to the single

molecule level, enable combination of biosensors and optogenetics, and study low abundance molecules by greatly reducing cell perturbation.

- Hahn, K.M., R. DeBiasio and D.L. Taylor. Patterns of elevated free calcium and calmodulin activation in living cells. **Nature**, 359: 736-738, 1992.
- Kraynov, V. S., C. E. Chamberlain, G. M. Bokoch, M. A. Schwartz, S. Slabaugh and K.M. Hahn. Localized Rac Activation Dynamics Visualized in Living Cells. **Science**, 290:333-337, 2000.
- Pertz, O., Hodgson, L., Klemke, R., and Hahn, K.M. Spatio-temporal dynamics of RhoA activity in migrating cells. **Nature**, 440:1069-1072, 2006.
- Koivusalo, M., Welch, C., Hayashi, H., Scott, C.C., Kim, M., Alexander, T., Touret, N., Hahn, K.M., and Grinstein, S. Amiloride inhibits macropinocytosis by lowering submembranous pH and preventing Rac1 and Cdc42 signalling. **J. Cell Biol.**, 188: 547-563, 2010. PMC2828922

Optogenetics. Optogenetics began with the engineering of light-sensitive ion channels to control brain function, but more recently completely different designs have enabled control of other protein families critical to cell physiology (eg GTPases, kinases, scaffolds). We were among the first to focus on non-channel optogenetics, controlling GTPases with light in living cells. We have developed alternate approaches for optogenetic control that are suitable for different protein families, and with complementary advantages (PA-GTPases, LOVTRAP, insertion of photoresponsive domains for allosteric control). Our molecules have been valuable to study information flow in motility and immune cells (our work), to control the movement of cells in living animals, and for studies in development, immunology and brain function.

- 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
- Wang, X. He, L., Wu, Y., Hahn, K. M., and Montell, D. 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. PMC2929827
- Hayashi-Takagi, A., Yagishita, S., Nakamura, M., Shirai, F., Wu, Y.I., Loshbaugh, A.L., Kuhlman, B., Hahn, K.M., and Kasai, H. Labelling and optical erasure of synaptic memory traces in the motor cortex. **Nature** 525:333-338, 2015. PMC4634641.
- Wang, H., Vilela, M., Winkler, A., Tarnawski, T., Schlichting, I., Yumerefendi, H., Kuhlman, B., Liu, R., Danuser, G., and Hahn, K.M. LOVTRAP, An Optogenetic System for Photo-induced Protein Dissociation. **Nature Methods**, 13(9): 755-8, 2016.

Engineered allosteric responses. Using insights gained from our studies of protein allostery, we have developed engineered protein domains that can be inserted into proteins to confer regulation by light or small molecules. In our work published to date, we have generated inert, catalytically inactive kinases which be activated in living cells and animals by adding a small molecule to the medium or circulation. Kinases can be directed to interact only with specific substrates upon activation. We and others have used these tools to elucidate networks that control cell morphodynamics, metastasis and immune function. The kinase activation has essentially absolute specificity, so has been useful to differentiate the functions of very similar proteins, altering their function without the compensation seen when using genetic manipulation.

- Karginov, A., 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
- 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
- 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. **Nat. Chem. Bio.** 10(4):286-90, 2014. PMC40647t90
- Dagliyan, O., Tarnawski, M., Chu, P-H., Shirvanyants, D., Schlichting, I., Dokholyan, N.V., and Hahn, K.M. Engineering extrinsic disorder to control protein activity in living cells. **Science**. 354(6318):1441-1444, 2016.

Fluorescent dyes that report protein function *in vivo*. My lab has developed environment-sensing fluorescent dyes to interrogate signaling activity in living cells and animals. When attached to proteins, their fluorescence responds to protein conformational changes or post-translational modifications. Biosensors based on the dyes provide greater sensitivity than FRET because they are directly excited, are very bright ($\epsilon > 150,000$, QY > 0.7), and fluoresce at wavelengths > 600 nm. We and other have used the dyes to quantify the conformational state of endogenous proteins. Our studies of photobleaching and dye response mechanisms have been valuable in the design of fluorophores by other laboratories. New dyes are being designed for single molecule and super-resolution microscopy within living cells.

- Touthkine, A., V. Kraynov, and K. M. Hahn. Solvent-Sensitive Dyes to Report Protein Conformational Changes in Living Cells, **J. Amer. Chem. Soc.**, 125:4132-4145, 2003.
- Nalbant, P., L. Hodgson, V. Kraynov, A. Touthkine, K. M. Hahn. Activation of Endogenous Cdc42 Visualized in Living Cells. **Science**, 305:1615-1619, 2004.
- Touthkine, A., Han, W.G., Ullmann, M., Liu, T., Bashford, D., Noodleman, L., and Hahn, K.M. Experimental and DFT studies: novel structural modifications greatly enhance the solvent sensitivity of live cell imaging dyes. **J Phys Chem A**. 111:10849-60, 2007. PMC3742023
- Gulyani, A., Vitriol, E., Allen, R., Wu, J., Gremyachinskiy, D., Lewis, S., Dewar, B., Graves, L.M., Kay, B.K., Kuhlman, B., Elston T., and Hahn, K.M. A biosensor generated via high-throughput screening quantifies cell edge Src dynamics. **Nature Chem. Biol.**, 7: 437-444, 2011. PMC3135387

GTPase signaling. My lab has used the above tools together with “traditional approaches” to elucidate Rho family function in cell biology. These studies elucidated the pathways mediating apoptosis in response to cell damage and receptor ligation, dissected the role of GTPases in the control of cytoskeletal dynamics, and now are being used to elucidate the role of “Rho family networks” in immune cell function and metastasis.

- Subauste, M., O. Pertz, E. Adamson, C. E. Turner, S. Junger, K. M. Hahn. Vinculin modulation of Paxillin-FAK interactions regulates ERK to control survival and motility. **J. Cell Biol.**, 165:171-181, 2004. PMC2172187
- Machacek, M., Hodson, 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
- 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: 226-236, 2010. PMC2824622
- Hodgson, L., Spiering, D., Sabouri-Ghomi, M., DerMardirossian, C., Danuser, G., and Hahn, K.M. FRET binding antenna reports spatiotemporal dynamics of GDI-Cdc42 GTPase interactions. **Nature Chem. Biol.**, 2016. doi: 10.1038/nchembio.2145. [Epub ahead of print].

Complete List of Published Work in MyBibliography

<http://www.ncbi.nlm.nih.gov/sites/myncbi/klaus.hahn.1/bibliography/40336082/public/?sort=date&direction=ascending>