BIOGRAPHICAL SKETCH

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NAME: Howe, Alan K.

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

POSITION TITLE: Professor, Dept. of Pharmacology; Adjunct Prof, Dept. of Molecular Physiology & Biophysics

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 New Hampshire, Durham NH	B.S.	06/1990	Biochemistry
Northwestern University, Chicago IL	Ph.D.	09/1996	Tumor Cell Biology
University of North Carolina – Chapel Hill NC	Postdoctoral	07/2003	Pharmacology

A. Personal Statement

My laboratory has a long-standing interest in the mechanisms cells use to interpret & respond to their extracellular environment, with specific interest in the role of integrin-mediated adhesion to the extracellular matrix (ECM) in governing cell signaling, cytoskeletal dynamics, and cell migration. We were the first to demonstrate the subcellular regulation of Protein Kinase A (PKA) in the leading edge of motile cells and its requirement for efficient migration – a paradigm that we & others have extended and refined over the years. Recently, we have demonstrated that PKA is regulated by cell-ECM tension, is a functional component of focal adhesions, and is localized there in part through a mechanically-gated interaction with the archetypal focal adhesion protein talin. These observations establish an important role for localized PKA signaling in mechanotransduction and mechanically-guided migration. Through these efforts, we have become adept in using both microfluidics and tunable hydrogels to precisely manipulate physical, chemical, and mechanical aspects of 2- and 3-D cellular microenvironments and assessing the consequences of these manipulations on cell morphology, motility, and subcellular signaling events with high spatiotemporal resolution. We are currently applying these & other techniques to investigate the mechano-chemical regulation of PKA signaling during migration and delineate the targets and regulation of PKA within migration-associated subcellular niches such as focal adhesions. Through new collaborative projects, we are also investigating a new connection between cell tension, reactive oxygen species, and furious 'Ca^{2+} storms' in canonically non-excitable cells, the regulation of LKB1 – a principal activator of AMPK and a master regulator of cellular metabolism and polarity – by cell-matrix tension, and the molecular mechanisms through which certain kinesin-family motor proteins connect chromosome alignment to cell geometry, cell motility, and the response to chemotherapeutics.

<u>Ongoing and recent funding of note</u>:

1 R35 GM 153456-01 (Howe, P.I.) 08/01/24 – 04/31/29
Mechanical Regulation of PKA Function in Cell Adhesion and Migration
This project funds our laboratory's ongoing pursuit to understand how cells assemble and control 'solid-state' adhesion-related signaling complexes to convert mechanical information about their microenvironment into biochemical signals that control cell behavior.
Role: PI (6 calendar months)

1 R01 GM 143250-01A1 (Cunniff, P.I.) 08/01/23 – 07/31/27
NIH/NIGMS
Mitochondrial Positioning Regulates Redox-signaling During Cell Migration

This project will test the hypothesis that Miro1-mediated subcellular positioning of mitochondria induces localized redox-dependent signaling events to support cytoskeleton and FA dynamics.
Role: Co-I (1.2 calendar months until start of R35GM153456 on 08/01/24; unfunded collaborator thereafter)

1 R01 GM 137611-01A1 (Howe, P.I.) 09/10/21 – 08/31/23
NIH/NIGMS (*on nce until 08/31/24*)
Protein Kinase A in Focal Adhesions - Mechanisms and Consequences
This project will investigate the hypothesis, based on compelling preliminary data, that talin is a novel, mechanically-gated A-kinase anchoring proteins that localizes a discrete pool of PKA within focal adhesions to promote phosphorylation of talin and talin-associated proteins and thus modulate focal adhesion dynamics.
Role: PI (6 calendar months)

Published articles of note: (Total citations: 7913; h-index:33)
1. **Howe, A. K.**, Baldor, L. C., and Hogan, B. P. (2005) Spatial regulation of the cAMP-dependent protein kinase during chemotactic cell migration. *Proceedings of the National Academy of Sciences of the United States of America* **102**, 14320-14325. PMCID 1242330
2. McKenzie, A. J., Campbell, S. L., and **Howe, A. K.** (2011) Protein kinase A activity and anchoring are required for ovarian cancer cell migration and invasion. *PLoS One* **6**, e26552. PMCID 3197526
3. Cunniff, B., McKenzie, A. J., Heintz, N. H., and **Howe, A. K.** (2016) AMPK activity regulates trafficking of mitochondria to the leading edge during cell migration and matrix invasion. *Mol Biol Cell* **27**, 2662-2674. PMCID 5007087
4. McKenzie, A. J., Hicks, S. R., Svec, K. V., Naughton, H., Edmunds, Z. L., and **Howe, A. K.** (2018) The mechanical microenvironment regulates ovarian cancer cell morphology, migration, and spheroid disaggregation. *Sci Rep* **8**, 7228. PMCID 5940803
5. McKenzie, A. J., Svec, K. V., Williams, T. F., and **Howe, A. K.** (2020) Protein kinase A activity is regulated by actomyosin contractility during cell migration and is required for durotaxis. *Mol Biol Cell* **31**, 45-58. PMCID 6938270
6. Svec, K. V., and **Howe, A. K.** (2022) Protein Kinase A in cellular migration-Niche signaling of a ubiquitous kinase. *Front Mol Biosci* **9**, 953093. PMCID 9361040
7. Kang, M., Senatore, A.J., Naughton, H., McTigue, M., Beltman, R.J., Herppich, A.A., Pflum, MK.H., **Howe, A.K.** (2024) Protein Kinase A is a functional component of focal adhesions. *J. Biol Chem* **300**:107234
8. Kang, M., Otani, Y., Guo, Y., Yan, J., Goult, B.T., **Howe, A.K.** (2024) The focal adhesion protein talin is a mechanically-gated A-kinase anchoring protein. *Proc Natl Acad Sci USA* **121**:e2314947121

B. Positions, Scientific Appointments, and Honors

Positions and Employment

03/15/23 – Present	Assoc. Dir., Cancer Research Training and Education Coordination, UVM Cancer Center
07/01/19 – Present	Professor, Department of Pharmacology
07/01/19 – Present	Professor, Department of Molecular Physiology & Biophysics
07/01/09 – 06/30/19	Associate Professor, University of Vermont
02/01/13 – 09/01/13	Co-Leader, 'Tumor Progression & Host Factors' Program, Vermont Cancer Center
08/01/03 – 06/30/09	Assistant Professor, University of Vermont
08/01/01 – 07/31/03	Research Assistant Professor, University of North Carolina
09/01/96 – 07/31/01	Postdoctoral Research Assistant, University of North Carolina

Honors

2024	Inductee, Vermont Academy of Science & Engineering (VASE)
2019	Director's Award – UVM Cellular, Molecular & Biomedical Sciences Graduate Program
2018	Laureate Society, American Cancer Society
2018	Keynote Speaker (c/Dr. J. Stumpff), 20th Annual Women's Health & Cancer Conference
2010-2011	Nominee, Silver Stethoscope Award for Teaching Excellence, UVM College of Medicine
2010	Distinguished Alumnus Speaker, Lineberger Comprehensive Cancer Center
	Postdoctoral Fellow Training Grant, University of North Carolina at Chapel Hill
2001	Recipient, Howard Temin Career Award, National Cancer Institute/NIH
1999-2001	Postdoctoral Fellow, American Cancer Society

Patents

Phosphoprotein detection reagent and methods of making and using the same; U.S. Patent No. 7,799,526 (Licensed by Invitrogen™).

Other Experience and Professional Memberships

2015-Present	American Society for Biochemistry and Molecular Biology
2009-Present	American Association for Cancer Research
1998-Present	American Academy for the Advancement of Science
1996-Present	American Society for Cell Biology

External Academic Service

- *Ad hoc* reviewer: *Biochim Biophys Acta, Biology of the Cell*, *BMC Cancer, BMC Cell Biol, Cancer Res, Cell Death Differ, Cell Motil Cytoskel, Cell Reports, EMBO J, iScience, J Biol Chem, J Cell Biol, J Cell Phys, J Cell Sci, J Invest Derm, J Leuko Biol, JoVE, Matrix Biol, Mol Biol Cell, Mol Cancer Res, Nature, Nature Cell Biol, Nature Communications, Nature Signaling Gateway, Oncogene, Oncotarget, PLoS Genetics, PLoS ONE, PNAS, Review Commons, Science, Vasc Pharm*
- Associate Editor, Frontiers in Cell and Developmental Biology, section on Cell Adhesion and Migration (2023-Present)
- Regular member, Intercellular Interactions (ICI) NIH Study Section (2018-2022)
- Member (& Chair), Cell Structure & Metastasis Peer Review Committee, American Cancer Society (2011/2015-2018); *ad hoc* member, Cancer Cell Biology Peer Review Committee (2026-Present)
- Reviewer, Mission Boost Grant Program, American Cancer Society (2018-2022)
- Reviewer & Chair, Falk Medical Research Trust Awards, The Medical Foundation (2018-2021)
- Member, Cell Structure & Signaling Peer Review Study Group (National), American Heart Association
- *Ad hoc* member, NIH Study Sections: Molecular & Integrative Signal Transduction (MIST); Special Emphasis Panel (SEP) ZRG1 CB D(50)R - "Technologies for Single Cell Analysis"; ZRG1 OBT-K (02): Cancer Biology SEP; K99 Career Award Review Panel - ZDE1 RK 12 M; Cell Structure & Function-1 (CSF1); Special Emphasis Panel/Scientific Review Group 2026/05 ZRG1 BN-F (92) S
- *Ad hoc* grant reviewer, Molecular and Cellular Medicine Board, Medical Research Council, UK; French National Cancer Institute (INCa); Worldwide Cancer Research (formerly AICR); METAvivor Research and Support Inc.; Genetics Program – DEVCOM ARL Army Research Office; Alfred P. Sloan Foundation

C. Contributions to Science

1. As a postdoctoral fellow, I began my research into how cell adhesion to the extracellular matrix (ECM) controls cell signaling, shape, and function. I provided novel, significant insights into anchorage-dependent signaling through the MAPK cascade and also brought to the fore the important role of the cAMP-dependent protein kinase (PKA) as both a regulator of and an effector for adhesion-dependent signaling.
    a. **Howe, A.K.** and Juliano, R.L.. 2000. Regulation of anchorage-dependent signal transduction by protein kinase A and p21-activated kinase. *Nature Cell Biol*. **2**:593-600.
    b. **Howe, A.K.**. 2001. Cell adhesion regulates the interaction between Nck and p21-activated kinase. *J. Biol. Chem*. **276**:14541-14544.
    c. **Howe, A.K.,** Hogan, B.P., and Juliano, R.L. 2002. Regulation of vasodilator-stimulated phosphoprotein phosphorylation and interaction with Abl by protein kinase A and cell adhesion. *J. Biol. Chem*. **277**: 38121-38126
    d. **Howe, A.K.,** Aplin, A.E., Juliano R.L. 2002. Anchorage-dependent ERK signaling – mechanisms and consequences. *Curr Opin Genet Dev* **12**:30-35.

2. In my early independent career, I further investigated the role of PKA as a regulator of cell adhesion and cytoskeletal dynamics. My laboratory was the first to show that PKA is spatially regulated in migrating cells, with a specific up-regulation of activity within the leading edge. Moreover, we showed that inhibition of not only PKA activity but also of PKA localization through A-kinase anchoring proteins (AKAPs) blocks cell migration, as well as the ability of ovarian cancer cells to invade a three-dimensional ECM. Importantly, this work has provided a foundation upon which many labs (including our own) continue to validate, refine, and expand these core observations to reinforce the importance and complexity of PKA function in migration. Taken together, this work not only added to the lexicon of signaling pathways that are differentially regulated within subcellular space during cell migration, but

firmly established PKA as a central regulator of diverse aspects of adhesive and cytoskeletal events at the leading edge.

a. **Howe, A.K.**, Baldor, L.C., and Hogan, B.P. 2005. Spatial regulation of cAMP-dependent protein kinase during chemotaxis. *Proc. Natl. Acad. Sci. USA* **102**:14320-14325.
b. **Howe, A.K.** (2011) Cross-talk between calcium and protein kinase A in the regulation of cell migration. *Curr. Opin. Cell Biol.* **23**:554-61.
c. *McKenzie, A.J., Campbell, S.L., **Howe, A.K.** (2011) Protein kinase A activity and anchoring are required for ovarian cancer cell migration and invasion. *PLoS ONE*.**6**(10):e26552. (*Selected as a "Must Read" by the Faculty of 1000).
d. Svec, K.V. and **Howe, A.K.** (2022) Protein Kinase A in cellular migration-Niche signaling of a ubiquitous kinase. *Front Mol Biosci* **9**:953093.
e. Svec, K.V., Kang, M., and **Howe, A.K.** (2023) Protein Kinase A Activity in the Leading Edge of Migrating Cells is Dependent on the Activity of Focal Adhesion Kinase. *Submitted to Review Commons; available on BioRxiv (https://www.biorxiv.org/content/10.1101/2022.09.17.508387v1)*
f. Kang, M., Senatore, A.J., Naughton, H., McTigue, M., Beltman, R.J., Herppich, A.A., Pflum, MK.H., **Howe, A.K.** (2024) Protein Kinase A is a functional component of focal adhesions. *J. Biol Chem* **300**:107234
g. Kang, M., Otani, Y., Guo, Y., Yan, J., Goult, B.T., **Howe, A.K.** (2024) The focal adhesion protein talin is a mechanically-gated A-kinase anchoring protein. *Proc Natl Acad Sci USA* **121**:e2314947121

3. My laboratory has also contributed to the burgeoning field of mechanobiology. Our studies have established a dynamic, reciprocal relationship between fibroblast contractility and the tension of their surrounding connective tissue matrix. These early collaborative studies 'crossed-over' into the more central focus of my laboratory and we have begun to use cutting edge experimental approaches (*e.g.* engineered 3D ECMs, microfluidics & microfabrication, traction force microscopy) in funded efforts to explore the coordinate regulation of localized PKA and cellular tension during cell migration.
    a. Langevin, H.M., Nedergaard, M., and **Howe, A.K.** (2013) Cellular control of connective tissue matrix tension. *J. Cell. Biochem* **114**(8):1714-9.
    b. McKenzie, A.J., Hicks, S.R., Svec, K.V., Naughton, H., Edmunds, Z.L., and **Howe, A.K.** (2018) The mechanical microenvironment regulates ovarian cancer cell morphology, migration, and spheroid disaggregation. *Sci Rep* **8**:7228.
    c. McKenzie, A.J., Svec, K.V., Williams, T.F., and **Howe, A.K.** (2020) Protein kinase A activity is regulated by actomyosin contractility during cell migration and is required for durotaxis. *Mol Biol Cell* **31**:45-58.
    d. Kang, M., Otani, Y., Guo, Y., Yan, J., Goult, B.T., **Howe, A.K.** (2024) The focal adhesion protein talin is a mechanically-gated A-kinase anchoring protein. *Proc Natl Acad Sci USA* **121**:e2314947121

4. Through a collaboration with Drs. Nick Heintz and Brian Cunniff, we demonstrated that mitochondria actively infiltrate leading edge lamellipodia, increasing local mitochondrial mass and relative ATP concentration, and supporting a localized reversal of the Warburg Effect. This influx and metabolic shift correlate with increased pseudopodial activity of AMPK, a critical cellular energy sensor and metabolic regulator. Also, localized activation of AMPK increases leading edge mitochondrial flux, ATP content, and cytoskeletal dynamics, whereas optogenetic inhibition of AMPK halts mitochondrial trafficking during both migration and three-dimensional extracellular matrix invasion. These observations indicate that AMPK couples local energy demands to subcellular targeting of mitochondria during cell migration.
    a. Cunniff, B., McKenzie, A.J., Heintz, N.H., and **Howe, A.K.** (2016) AMPK activity regulates trafficking of mitochondria to the leading edge during cell migration and matrix invasion. *Mol. Biol. Cell* 27:2662-74. (*Featured on the issue cover and selected as a 'Highlights from MBoC' selection).

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