BIOGRAPHICAL SKETCH

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NAME: Howe, Alan K.

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

POSITION TITLE: Associate 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 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 how various signaling pathways & cytoskeletal dynamics are regulated in subcellular space during migration and matrix invasion. We employ and develop a wide variety of cutting-edge techniques for visualizing & quantifying dynamic, migration-related cytoskeletal changes and signaling events at the cellular and subcellular level. Recently, we have become increasingly adept in using both microfluidics, micro-contact printing, 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.

B. Positions and Honors

Positions and Employment

09/01/96 – 07/31/01	Postdoctoral Research Assistant, University of North Carolina
08/01/01 – 07/31/03	Research Assistant Professor, University of North Carolina
08/01/03 – 06/30/09	Assistant Professor, University of Vermont
07/01/09 – Present	Associate Professor, University of Vermont
02/01/13 – Present	Co-Leader, 'Tumor Progression & Host Factors' Program, Vermont Cancer Center

Honors

1999-2001	Postdoctoral Fellow, American Cancer Society
2001	Recipient, Howard Temin Career Award, National Cancer Institute/NIH
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

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

1996-Present	American Society for Cell Biology

1998-Present American Academy for the Advancement of Science
2009-Present American Association for Cancer Research

Academic Service

- *Ad hoc* reviewer: *J Cell Biol, J Cell Sci, Nature Cell Biol, Nature Signaling Gateway, Mol Biol Cell, Cancer Res, J. Invest Derm, J Leuko Biol, JoVE, Biochim. Biophys Acta, Vasc Pharm, Cell Death Differ, Cell Motil Cytoskel, J Biol Chem, Mol Cancer Res, Oncogene, Nature, Science, BMC Cancer, BMC Cell Biol, PLoS Genetics, PLoS ONE*
- Chair, Cell Structure & Metastasis Peer Review Group, American Cancer Society
- Member, Cell Structure & Signaling Peer Review Study Group (National), American Heart Association
- *Ad hoc* member, NIH Study Sections: Intercellular Interactions (ICI); 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
- *Ad hoc* reviewer, Molecular and Cellular Medicine Board, Medical Research Council, UK

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.** 2004. Regulation of actin-based cell migration by cAMP and PKA (Review). *Biochim. Biophys. Acta* **1692**:159-174.
    b. **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.
    c. **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.
    d. *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).

3. Through a long-standing & fruitful collaboration with Dr. Helene Langevin, I have 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. Of particular importance, these collaborative studies have '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. Three manuscripts describing our initial observations are (as of October, 2015) in active preparation and/or revision, and these early successes have reinforced our interest, focus, and commitment to understanding the interplay between cellular forces and localized signaling events during cell migration.

a. Langevin, H.M., Storch, K.N., Snapp, R.R., Bouffard, N.A., Badger, G.J., **Howe, A.K.**, Taatjes, D.J.. 2010. Tissue stretch induces nuclear remodeling in connective tissue fibroblasts. *Histochem Cell Biol*. **133**:405-15. PMC2880391
b. Langevin H.M., Bouffard N.A., Fox J.R., Palmer B.M., Wu J., Iatridis J.C., Barnes W.D., Badger, G.J., and **Howe, A.K.**. (2011) Fibroblast cytoskeletal remodeling contributes to connective tissue tension. *J. Cell. Physiol*. **226**:1166-75. PMC3053527
c. Abbott, R.D., Koptiuch, C. Iatridis, J.C., **Howe, A.K.**, Badger, G.J., Langevin, H.M.. (2013) Stress and matrix-responsive cytoskeletal remodeling in fibroblasts. *J. Cell. Physiol* **228**:50-7. PMC3414643
d. Langevin, H.M., Nedergaard, M., and **Howe, A.K.** (2013) Cellular control of connective tissue matrix tension. *J. Cell. Biochem* **114**(8):1714-9.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/alan.howe.1/bibliography/40326217/public/?sort=date&direction=ascending.D. Research Support

D. Research Support

Active

1 R01 GM 117490-01 (Howe, P.I.) 01/01/16 – 12/31/20
NIH/NIGMS
Mechano-Chemical Regulation of GPCR/PKA Signaling During Cell Migration
This project will delineate the mechanism coupling cellular tension to localized, ligand-dependent activation of canonical G-protein coupled receptor signaling.
Role: Principal Investigator

R01 GM097495-01 (Howe, P.I.) 09/01/11 – 08/31/15
NIH/NIGMS *on NCE until 08/31/16*
Cross-talk between PKA, cellular tension, and Ca^{2+} channels during cell migration
This project will explore the mechanisms underlying mechanosensitive PKA signaling & stretch-activated Ca^{2+} channels (SACCs) during cell migration
Role: Principal Investigator

5 R01 GM117839-06 (M. Thali, P.I.)* 08/01/15 – 07/31/19
NIH/NIGMS
Multiscale analysis of HIV-1 assembly, release, and cell-to-cell transmission
The overall goal of this proposal is to elucidate how cell-intrinsic and environmental factors regulate HIV-1 Env-induced cell-cell fusion and to test if small T cell-based syncytia contribute to virus spread and pathogenicity.
Role: Collaborator

Susan G. Komen Foundation 09/01/16 – 08/31/19
Investigating Kif18A as a therapeutic target for triple negative breast cancer
This project will investigate the role of the mitotic kinesin Kif18A in cell division, cell motility, and radiosensitization of TNBC cells.
Role: Collaborator (Jason Stumpff (UVM), PI)

University of Vermont Cancer Center 09/01/15 – 08/31/16
Lake Champlain Cancer Research Organization Pilot Grant Program
Investigating Kif18A as a therapeutic target for colorectal cancer
This project will investigate the role of the mitotic kinesin Kif18A in cell division, cell motility, and radiosensitization of colorectal cancer cells.
Role: Collaborator (Jason Stumpff (UVM), PI)

Completed
University of Vermont Cancer Center 05/01/14 – 04/31/15
Pilot Grant Program
Regulation of breast cancer osteomimicry by extracellular matrix rigidity
This project will determine whether ECM rigidity regulates the expression of Runx2, a master regulator of bone cell differentiation, and the osteomimicry program in metastatic breast cancer cells.
Role: Principal Investigator (G. Stein (UVM), co-I)

University of Vermont College of Medicine 07/01/12 – 06/30/14
Internal Grant Program
Microtubule-based transport of mitochondria during cell migration: mechanism and consequences
This project will investigate how mitochondria are targeted to the leading edge of migrating cells and determine what their role is in local regulation of cytoskeletal dynamics and cell migration.
Role: Principal Investigator (N. Heintz (UVM), co-I)

U. Mass/Dartmouth/Vermont Cancer Centers Collaborative Research Program 10/01/11 – 09/30/14
Protein Kinase A and mechanotransduction in ovarian cancer pathogenesis
The proposed work will investigate the role of PKA activity and anchoring in OvC dissemination in vivo and examine how the rigidity of tissues to which OvC spreads affects OvC cell migration & invasion.
Role: Principal Investigator (B. Berwin (Dartmouth); co-PI)

R01 AT001121-06 (Langevin, P.I.) 05/01/08 – 04/30/13
NIH/NCCAM
Connective Tissue Mechanotransduction
This work will investigate the active fibroblast response to tissue stretch by characterizing the mechanotransduction mechanisms linking cytoskeletal remodeling to signaling and gene expression.
Role: Collaborator

R01 GM074205-01 and GM074205-05S1 (Howe) 06/01/05 – 04/30/11 (no-cost extension from 04/30/10)
NIH/NIGMS
Spatial Regulation of Protein Kinase A in Cell Migration
This project determined the mechanism through which PKA is localized and activated specifically within the leading edge of migrating fibroblasts and to identify leading edge PKA substrates.
Role: PI

5 K01 CA 92237-01 (Howe, PI) 08/01/01 – 07/31/07 (no-cost extension from 07/31/06)
NIH/NCI (Howard Temin Career Award)
Regulation of Adhesion-Dependent Signaling by PKA and PAK.
The goals of this project were to (1) investigate the mechanism(s) through which PKA and PAK regulate the anchorage-dependent cellular response to growth factors and (2) investigate their significance in cell growth and cell motility.
Role: PI