BIOGRAPHICAL SKETCH

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NAME: Haynes, Jennifer

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

POSITION TITLE: Research Assistant 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
University of British Columbia, BC, Canada	B.Sc.	05/1999	Cell Biology and Genetics
University of Toronto, ON, Canada	Ph.D.	06/2006	Molecular and Medical Genetics
University of Toronto, ON, Canada	Postdoctoral	09/2007	Chemical Genetics and Genomics
University of California, San Francisco, CA	Postdoctoral	07/2011	Cell and Cancer Biology

A. Personal Statement

I have a broad background in cell and molecular biology and genetics, with specific training and expertise in intestinal stem cell biology and three-dimensional organoid culture. I have more than six years of experience in generating and utilizing patient-derived organoid culture models from intestinal tissue (normal and disease). Thus, I have the technical skill, expertise, and knowledge necessary to successfully carry out the proposed research. Starting from early on in my career, I have demonstrated proficiency in teamwork and collaboration. This has led to numerous publications in reputable peer-reviewed scientific journals. I also have experience in managing research projects, supervising and training others, and mentoring students. My current research interest in understanding the molecular mechanisms underlying alterations in nutrient and electrolyte transport in human disease states, and developing therapeutics that target absorption pathways, makes me well-suited for my role in this project.

1. **Haynes J**, Palaniappan B, Sundaram U. (2019) Establishment of Long-term Normal Human Intestinal Epithelial Organoid Cultures to Study the Regulation of Intestinal Nutrient and Electrolyte Transporters. Gastroenterology 156(6): S-270. Digestive Disease Week, San Diego, CA (*poster presentation*).
2. Lima-Fernandes E, Murison A, Medina T, Wang Y, Ma A, Leung C, Luciani G, **Haynes J**, Pollett A, Zeller C, Duan S, Kreso A, Barsyte-Lovejoy D, Wouters BG, Jin J, De Carvalho DD, Lupien M, Arrowsmith CH, O'Brien CA. (2019) Targeting bivalency de-represses Indian Hedgehog and inhibits self-renewal of colorectal cancer-initiating cells. Nat Commun 10(1):1436. PMCID: PMC6441108.
3. **Haynes J**, McKee TD, Haller A, Wang Y, Leung C, Gendoo D, Lima-Fernandes E, Kreso A, Wolman R, Szentgyorgyi E, Vines DC, Haibe-Kains B, Wouters BG, Metser U, Jaffray DA, Smith MJ, O'Brien CA. (2018) Administration of Hypoxia-Activated Prodrug Evofosfamide after Conventional Adjuvant Therapy Enhances Therapeutic Outcome and Targets Cancer-Initiating Cells in Preclinical Models of Colorectal Cancer. Clin Cancer Res 24(9): 2116-2127.

B. Positions and Honors

Positions and Employment

2004-2005	Teaching Assistant, Department of Medical Genetics and Microbiology, University of Toronto, Toronto, ON, Canada
2006-2007	Postdoctoral Fellow, Banting and Best Department of Medical Research, University of Toronto, Toronto, ON, Canada
2007-2011	Postdoctoral Fellow, Department of Cell and Tissue Biology, University of California, San Francisco, San Francisco, CA
2011-2014	Research Associate, Campbell Family Institute for Breast Cancer Research, Ontario Cancer Institute, Toronto, ON, Canada
2014-2018	Scientific Associate, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada
2018-	Research Assistant Professor, Department of Clinical and Translational Sciences, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV

Other Experience and Professional Memberships

2008-2011	Member, American Society for Cell Biology
2018-	Member, American Gastroenterological Association
2019-	Ad hoc Journal Reviewer, Biomolecules, Cancer Cell International, International Journal of Molecular Sciences, Journal of Clinical Medicine, Medicina, Stem Cell Research
2019	Grant Reviewer, University of Kentucky Center for Clinical and Translational Science
2020-	Member, Reviewer Board, Cancers

Honors

1999	Dean's Honor List, University of British Columbia, BC, Canada
1999	Adam F. Szczawinski Prize in Botany, University of British Columbia, BC, Canada
1999-2001	University of Toronto Open Fellowship, University of Toronto, ON, Canada
2000-2001	Ontario Graduate Scholarship in Science and Technology, University of Toronto, ON, Canada
2001-2002	Connaught Scholarship, University of Toronto, ON, Canada
2001-2002	Ontario Graduate Scholarship, Province of Ontario, Canada
2002-2005	Estate of Betty Irene West/Canadian Institutes of Health Research Doctoral Research Award
2008-2011	Terry Fox Foundation Post PhD Research Fellowship, Canadian Cancer Society Research Institute
2009	Outstanding Poster Award, The EMT International Association Meeting, Tucson, AZ
2011	Keystone Symposia Scholarship, Conference on Epithelial Plasticity and Epithelial to Mesenchymal Transition, Vancouver, BC, Canada

C. Contributions to Science

1. **Exploration of essential gene functions and the essential synthetic genetic network.** For my doctoral studies, I used budding yeast as a model organism to explore essential gene functions using titratable promoter-replacement alleles. My co-investigators at the University of Toronto created promoter-shutoff strains for over two-thirds of all essential yeast genes, for which deletion mutation (knockout) strains were inviable. I performed morphological analysis and cell size profiling for ~600 of these strains, which when combined with my co-investigators' data from drug sensitivity screening and microarray expression profiling was used to identify new functions for several previously uncharacterized genes. As a collaborative team, we further used these promoter-shutoff strains for automated, high-throughput genetic analysis and established a genetic interaction network for essential yeast genes.

    a. Mnaimneh S*, Davierwala AP*, **Haynes J***, Moffat J, Peng WT, Zhang W, Yang X, Pootoolal J, Chua G, Lopez A, Trochesset M, Morse D, Krogan NJ, Hiley SL, Li Z, Morris Q, Grigull J, Mitsakakis N, Roberts CJ, Greenblatt JF, Boone C, Kaiser CA, Andrews BJ, Hughes TR. (2004) Exploration of essential gene functions via titratable promoter alleles. Cell 118(1): 31-44 (**indicates equal contribution*).

b. Davierwala AP, **Haynes J**, Li Z, Brost RL, Robinson MD, Yu L, Mnaimneh S, Ding H, Zhu H, Chen Y, Cheng X, Brown GW, Boone C, Andrews BJ, Hughes TR. (2005) The synthetic genetic interaction spectrum of essential genes. Nat Genet. 37(10): 1147-52.

2. **The impact of protein-protein interaction affinity on biological activity depends on context.** In addition to the research described above, I also studied conserved cellular processes including signal transduction, transcriptional regulation, and cytoskeleton remodeling. Most cellular functions require protein-protein interactions, yet little was known about the relationship between protein-protein interaction affinity and biological activity. Together with my co-investigators, I investigated the role of binding affinity in SH3 domain-mediated protein-protein interactions involved in regulating signal transduction or actin cytoskeleton function in yeast. We demonstrated that in the context of a signal transduction pathway, binding affinity correlated to in vivo output, signaling pathway fidelity, and growth. However, in the context of actin cytoskeleton regulation, we found that considerable reductions in binding affinity did not affect growth even when the actin cytoskeletal morphology was significantly perturbed. Furthermore, the biological impact varied depending on the genetic and environmental context.

    a. Marles JA, Dahesh S, **Haynes J**, Andrews BJ, Davidson AR. (2004) Protein-protein interaction affinity plays a crucial role in controlling the Sho1p-mediated signal transduction pathway in yeast. Mol Cell 14(6): 813-23.
    b. **Haynes J**, Garcia B, Stollar EJ, Rath A, Andrews BJ, Davidson AR. (2007) The biologically relevant targets and binding affinity requirements for the function of the yeast Abp1p Src-homology 3 domain vary with genetic context. Genetics 176: 193-208. PMCID: PMC1893037

3. **Understanding the molecular regulation of cancer cell epithelial-mesenchymal transition (EMT) and metastasis.** Upon completion of my doctoral studies, the primary focus of my research became cancer cell biology, specifically understanding the molecular mechanisms governing EMT and tumor cell metastasis. Using high-resolution live cell imaging, my UCSF co-investigators and I analyzed the regulated dynamics of actin cytoskeleton remodeling during EMT of mammary epithelial cells in culture. We identified novel and non-redundant functions for mammalian ERM cytoskeleton-membrane linker proteins in regulating actin cytoskeleton organization and cell migration during EMT. Since actin cytoskeleton remodeling promotes morphological changes and cell migration during EMT and is also required for tumor cell metastasis, factors controlling this process are potentially key targets for cancer therapeutics.

    I continued research in this field at the Ontario Cancer Institute in Toronto, where I investigated the role of actin cytoskeleton regulators and polarity proteins in maintaining normal mammary epithelial cell-cell cohesion, using both two-dimensional (monolayer) and three-dimensional cell culture systems. Together with my co-investigators, I also developed an epithelial lineage reporter system to assess the contribution of basal and luminal cells to cancer cell invasion and metastasis. Using a metastatic mouse tumor cell line engineered to express our lineage reporters, we demonstrated that cells expressing the basal but not luminal reporter were both highly invasive in three-dimensional culture and metastatic in vivo. My co-investigators used this reporter system to identify a new driver of cell invasion whose expression correlates with decreased relapse-free survival in patients with TP53 wild-type breast cancer.

    a. **Haynes J**, Srivastava J, Madson N, Wittmann T, Barber D. (2011) Dynamic actin remodeling during epithelial-mesenchymal transition depends on increased moesin expression. Mol Biol Cell 22(24): 4750-64. PMCID: PMC3237619
    b. Sonzogni O, **Haynes J**, Seifried LA, Kamel YM, Huang K, BeGora MD, Au Yeung F, Robert-Tissot C, Heng Y, Yuan X, Wulf GM, Kron KJ, Wagenblast E, Lupien M, Kislinger T, Hannon GJ, Muthuswamy SK. (2018) Reporters to mark and eliminate basal or luminal epithelial cells in culture and in vivo. PLoS Biol 16(6): e2004049. PMCID: PMC6042798

4. **Therapeutic targeting of colorectal cancer stem cells (CSCs) in patient-derived models.** During my most recent studies, I investigated new therapeutic strategies for targeting colorectal CSCs. Standard-of-care chemotherapy agents for colorectal cancer have previously been shown to target more differentiated cancer cells while sparing the CSC fraction. By a combined in vitro/in vivo approach using patient-derived models, my co-investigators and I determined that hypoxia drives the formation of colorectal CSCs and that cells surviving conventional therapy are more hypoxic and CSC-like. Using a novel approach to

combination therapy, we showed that sequential treatment with conventional therapy followed by a hypoxia-activated prodrug both inhibited xenograft tumor growth and also decreased the colorectal CSC fraction. Furthermore, we identified a biomarker for hypoxia that can be used to identify colorectal cancers that will benefit most from the addition of a hypoxia-activated prodrug.

In addition, I was the first investigator at my institute to successfully and routinely generate human three-dimensional organoid cultures from surgically resected tissue. In total, I established a panel of >10 long-term human epithelial organoid cultures from normal colon tissue and >30 from colorectal cancer tissue. These tumor organoid models will better represent the diverse nature of the disease compared to traditional cell culture models and are currently being used in multiple collaborative research projects, including high-throughput drug screens. The first manuscript employing our human colorectal cancer organoids was published just last year.

a. **Haynes J**, McKee TD, Haller A, Wang Y, Leung C, Gendoo D, Lima-Fernandes E, Kreso A, Wolman R, Szentgyorgyi E, Vines DC, Haibe-Kains B, Wouters BG, Metser U, Jaffray DA, Smith MJ, O'Brien CA. (2018) Administration of Hypoxia-Activated Prodrug Evofosfamide after Conventional Adjuvant Therapy Enhances Therapeutic Outcome and Targets Cancer-Initiating Cells in Preclinical Models of Colorectal Cancer. Clin Cancer Res 24(9): 2116-2127.
b. Rehman S, **Haynes J**, Lima-Fernandes E, Puri A, Haller A, Leung C, Agro L, Wang Y, O'Brien CA. (2016) Colorectal Cancer Stem Cells. In book: Cancer Stem Cells: Targeting the Roots of Cancer, Seeds of Metastasis, and Sources of Therapy Resistance, edited by Liu H and Lathia J: 177-209.
c. Lima-Fernandes E, Murison A, Medina T, Wang Y, Ma A, Leung C, Luciani G, **Haynes J**, Pollett A, Zeller C, Duan S, Kreso A, Barsyte-Lovejoy D, Wouters BG, Jin J, De Carvalho DD, Lupien M, Arrowsmith CH, O'Brien CA. (2019) Targeting bivalency de-represses Indian Hedgehog and inhibits self-renewal of colorectal cancer-initiating cells. Nat Commun 10(1):1436. PMCID: PMC6441108

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/18m4R0RpMsbkD/bibliography/40522939/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

No ID Haynes (PI) 12/01/19-11/30/21
COBRE ACCORD Pilot Grant NIH
Regulation of human intestinal nutrient transporters by adipocyte-derived factors
The goal of this research is to determine the effect of adipocyte-derived factors on activity and expression of human intestinal epithelial cell nutrient transporters and identify potential regulatory pathways involved.