BIOGRAPHICAL SKETCH

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NAME: Bryant, Kirsten Leigh

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

POSITION TITLE: 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
Bucknell University, Lewisburg, PA	B.S.	05/2007	Biology
Cornell University, Ithaca, NY	Ph.D.	08/2013	Pharmacology
University of North Carolina at Chapel Hill, Chapel Hill, NC	Postdoc.	09/2018	Pharmacology

A. Personal Statement

My passion as a scientist is to perform research that contributes to a better understanding of pancreatic cancer biology and leads to improved treatments for this disease. My work focuses on the relatively unexplored mechanisms by which the *KRAS* oncogene drives the altered metabolic processes that fuel pancreatic cancer growth. During my final year in graduate school, I lost my father to pancreatic cancer. This experience made clear to me the dismal lack of options for pancreatic cancer patients and instilled in me a strong desire to pursue a more clinically relevant project for my postdoctoral studies. Thus, I joined the laboratory of Dr. Channing Der at the University of North Carolina at Chapel Hill (UNC-Chapel Hill), specifically to develop my knowledge and research skills in the field of pancreatic cancer. There I addressed the role of KRAS in the increased autophagic activity required for PDAC growth. This work won me funding including an AACR/Pancreatic Cancer Action Network Pathway to Leadership Grant (similar to the K99/R00 award; $600,000/6 years). In a comprehensive mechanistic study recently published in *Nature Medicine* (Bryant et al., 2019), I found that the genetic suppression of *KRAS* increased autophagic flux, as did pharmacological inhibition of its effector, ERK MAPK. This finding led me to conclude that concurrent inhibition of ERK and autophagy may be an effective PDAC treatment. Additionally, my autophagy study has invigorated interest in targeting autophagy for PDAC treatment and led to the initiation of clinical trials at MD Anderson Cancer Center, UNC-Chapel Hill and Harvard/DFCI. In my independent research, I am focused on improving our understanding of how best to target autophagy in RASdriven cancers, including determining whether dual targeting of the ERK MAPK pathway and autophagy is a therapy that translates to cancers other than PDAC and discovering new ways to induce and inhibit autophagy. I have recently been awarded an R37 MERIT award from the NCI to support these studies

In addition to my research activities, I am also very committed to mentoring younger scientists and to community outreach. I have directly mentored three undergraduates, one MS student, and eight PhD rotation students throughout the course of my graduate and postdoctoral studies. Each undergraduate that I mentored worked in the lab for more than two years and developed their own projects under my supervision. Additionally, I plan, organize and lead large-scale laboratory tours for groups of pancreatic cancer patients and their families in order for them to learn what their donations to pancreatic cancer research accomplish. I attend National Pancreatic Cancer Advocacy Day in Washington, D.C. yearly, where I serve as a scientific liaison for pancreatic cancer patients and families by aiding them in explaining scientific information during their meetings with

members of Congress. Overall, I am a committed pancreatic cancer biologist who has had success translating academic research into the clinic, securing research funding, and mentoring future scientists.

B. Positions and Honors

Positions:

2007 - 2013 Graduate Research Assistant, Cornell University
2013 - 2018 Postdoctoral Associate, UNC-Chapel Hill, Lineberger Comprehensive Cancer Center
2018 - present Assistant Professor, Department of Pharmacology, UNC-Chapel Hill
2020 - present Member, Lineberger Comprehensive Cancer Center, UNC-Chapel Hill

Other Experience and Professional Memberships:

2005 - 2007 Vice President of Public Relations, Bucknell University Biology Club 2011 - present Reviewer, *PLoS One*
2014 Judge, NC Student Academy of Science State Science Competition
2014 - present Reviewer, Molecular Cancer Therapeutics
2015 Judge, NC Student Academy of Science State Science Competition
2017 - 2019 Elected Member, UNC Lineberger ITCMS NCI T32 Postdoctoral Advisory Committee
2019 - present Member, BBSP Graduate Admissions Committee, UNC-Chapel Hill
2019 - present Reviewer, *Nature Communications*
2019 - present Reviewer, *Molecular Cancer Research*
2019 - present Reviewer, *Nature Communications*
2019 - present Reviewer, *Oncogene*
2020 - present Reviewer, *Gastroenterology*
2020 - present Member, Biological and Biomedical Sciences Program (BBSP) Graduate Program, UNCChapel Hill
2021 - present Reviewer, *Cancer Research*

Honors:

2002 Girl Scout Gold Award
2003 Alpha Lambda Delta Honor Society
2003 Valedictorian, Conrad Weiser High School, Robesonia, PA
2005 Mortar Board National Honors Society
2005 Phi Sigma Biological Honors Society
2007 Phi Sigma Biological Society Award, Bucknell University
2007 Phi Beta Kappa National Honors Society
2007 Sigma Xi Scientific Research Honors Society
2004-2007 President's Award for Distinguished Academic Achievement, Bucknell University
2014 Invited Poster Presenter, Vallee Foundation Symposium, Boston, MA
2011 BBS Symposium Conference Travel Grant, Cornell University
2015 Invited Participant, Cold Spring Harbor Laboratory Workshop in Pancreatic Cancer, Cold Spring Harbor, NY
2017 Best Talk Award, UNC Lineberger Postdoc-Faculty Research Day
2019 Joseph S. Pagano Award, University of North Carolina at Chapel Hill
2019 Scholar-In-Training Award, AACR Special Conference on Pancreatic Cancer: Advances in Science and Clinical Care, September 6-9, 2019, Boston, MA
2019 Keynote speaker, 2019 Pancreatic Cancer Action Network Annual Scientific Summit, October 2-4, 2019, Coral Gables, FL
2020 Invited Speaker and Session Chair, Experimental Biology 2020, Symposium: Recent Progress in Drugging the "Undruggable" RAS Oncogene, April 4-7, 2020, San Diego, CA *Cancelled due to COVID-19; Rescheduled for 2021
2020 Scholar Award, William Guy Forbeck Research Foundation

C. Contributions to Science

1. The role of KRAS in the increased autophagic activity required for PDAC growth. In a comprehensive mechanistic study (Bryant et al., *Nature Medicine* 2019), I found that the genetic suppression of KRAS increased autophagic flux, as did pharmacological inhibition of its effector, ERK MAPK. I supported this finding using autophagic flux assays, a large-scale Reverse Phase Protein Array (RPPA) analysis of ERKi treated PDAC cell lines, as well as a parallel RNA-Seq study. I speculated that ERK inhibition might enhance PDAC dependence on autophagy by impairing KRAS-driven metabolic processes. I utilized RNA-Seq data and metabolomics, among other techniques, to demonstrate that either *KRAS* suppression or ERK inhibition decreased both glycolytic and mitochondrial functions. Furthermore, I demonstrated that genetic or pharmacologic inhibition of autophagy synergistically enhanced ERK inhibitor-mediated anti-tumor activity. This finding led me to conclude that concurrent inhibition of ERK and autophagy may be an effective PDAC treatment. Based on this study, two clinical trials have been initiated by our group. One trial will be performed in collaboration with Dr. David Fogelman at MD Anderson Cancer Center, and is an investigator sponsored clinical trial with Array BioPharma to study the combination of their MEK inhibitor binimetinib and the autophagy inhibitor hydroxychloroquine. Another trial will be performed in collaboration with Drs. Autumn McRee at UNC and Brian Wolpin at the DanaFarber Cancer Institute to study the combination of the ERK inhibitor LY3214996 with hydroxychloroquine. We are currently extending these studies by determining whether inhibition of IGF-1R can further enhance the efficacy of this combination.

a. **Bryant KL**, Stalnecker CA, Zeitouni D, Klomp JE, Peng S, Tikunov AP, Gunda V, Pierobon M, Waters AM, George SD, Tomar G, Papke B, Hobbs GA, Yan L, Hayes TK, Diehl JN, Goode G, Chaika NV, Wang Y, Zhang GF, Witkiewicz AK, Knudsen ES, Petricoin EF 3rd, Singh PK, Macdonald JM, Tran NL, Lyssiotis CA, Ying H, Kimmelman AC, Cox AD, Der CJ. (2019) Combination of ERK and autophagy inhibition as a treatment approach for pancreatic cancer. *Nat Med* 25: 628-40. PMCID: PMC6484853.
    Highlighted in:
        1) Seton-Rogers S. (2019) Eliminating protective autophagy in KRAS-mutant cancers. *Nat Rev Cancer* 19:247.
        2) Dolgin E. (2019) Combo drug study tested for PDAC. *Cancer Discov* 9:571.
        3) Dickson I. (2019) Autophagy inhibitor combination strategies for pancreatic cancer. *Nat Rev Gastroenterol Hepatol* 16:262-263.
        4) Zhao H, Zheng B. (2019) Duel targeting of autophagy and MEK in KRAS mutant cancer. *Trends Cancer* 5:327-329.
        5) Dolgin, E. (2019) Anticancer autophagy inhibitors attract 'resurgent' interest. *Nat Rev Drug Discov* 18:408-410.
        6) Recommended in F1000Prime
a. Hobbs GA, Baker NM, Miermont AM, Thurman RD, Pierobon M, Tran TH, Anderson A, Waters AM, Diehl JN, Papke B, Hodge RG, Klomp JE, Goodwin CM, DeLiberty JM, Wang J, Ng R, Gautam P, **Bryant KL**, Esposito D, Campbell SL, Petricoin III EF, Simanshu DK, Aguiree AJ, Wolpin BM, Wennerberg K, Rudloff U, Cox AD, and Der CJ. (2020) Atypical $KRAS^{G12R}$ mutant is impaired in PI3K signaling and macropinocytosis in pancreatic cancer. *Cancer Discov* 10:104-123. PMCID: PMC6954322.
b. **Bryant KL**, Der CJ. (2019) Blocking autophagy to starve pancreatic cancer. *Nat Rev Mol Cell Biol* 20: 265.
c. **Bryant KL**, Mancias JD, Kimmelman AC, Der CJ. (2014) KRAS: feeding pancreatic cancer proliferation. *Trends Biochem Sci* 39: 91-100. PMCID: PMC3955735.

2. Cytotoxic combinations with RAF and ERK inhibitors in PDAC. In a major collaborative project currently in the final stages of preparation for submission to *Cancer Research*, we aimed to identify therapeutic agents that would synergistically trigger apoptosis in cancer cells when used in combination with inhibitors of KRAS effector signaling. We performed a 525-drug chemical biology screen to identify combinations that enhanced the cytotoxic activity of clinical candidate/approved inhibitors of the RAF-MEK-ERK and the PI3K-AKT-mTOR effector pathways. Many more such combinations were identified for the former than for the latter, and the same classes of inhibitors were identified for inhibitors of the RAF, MEK and ERK nodes of the MAPK

cascade. We found that inhibitors of the PI3K-AKT-mTOR pathway, microtubules, HDAC and HSP90 each synergistically enhanced the cytotoxicity of RAF and ERK inhibitors, in both conventional and PDX-derived PDAC cell lines, in both anchorage-dependent and anchorage-independent culture systems. Mechanistically, we found that these combinations increased cellular apoptosis and slowed the cell cycle. A shared basis for synergy was the enhanced loss of MYC protein, a key ERK substrate and contributor to dysregulated PDAC metabolism. This project builds on the experience that I have gained studying the mechanisms that mediate the effects of ERK inhibition and PDAC as well as resistance mechanisms that arise in response to ERK inhibitor treatment.

a. Goodwin CM, Ozkan-Dagliyan I, George SD, Gautam P, Lucas KE, Papke B, Catalan-Hurtado R, Javaid S, Khatib T, Wennerberg K, Cox AD, **Bryant KL***, Der CJ*. Combinatorial inhibition of KRAS effector signaling in KRAS-mutant cancer. *Cancer Res*, In Preparation. *co-authorship.
b. Vaseva AV, Blake DR, Gilbert TSK, Ng S, Hostetter G, Azam SH, Ozkan-Dagliyan I, Gautam P, **Bryant KL**, Pearce KH, Herring LE, Han H, Graves LM, Witkiewicz AK, Knudsen ES, Pecot CV, Rashid N, Houghton PJ, Wennerberg K, Cox AD, Der CJ. (2018) KRAS suppression-induced degradation of MYC is antagonized by a MEK5-ERK5 compensatory mechanism. *Cancer Cell*, 34: 807-822. PMCID: PMC6321749.
c. Hayes TK, Neel NF, Hu C, Gautam P, Chenard M, Long B, Aziz M, Kassner M, **Bryant KL**, Pierobon M, Marayati R, Kher S, George SD, Xu M, Wang-Gillam A, Samatar AA, Maitra A, Wennerberg K, Petricoin EF 3rd, Yin HH, Nelkin B, Cox AD, Yeh JJ, Der CJ. (2016) Long-term ERK inhibition in KRAS-mutant pancreatic cancer is associated with MYC degradation and senescence-like growth suppression. *Cancer Cell* 29:75-89. PMCID: PMC4816652.

3. A novel EGFR mutant with oncogenic potential. My work as a graduate student focused on my discovery and characterization of a constitutively active, endoplasmic reticulum (ER)-retained epidermal growth factor receptor (EGFR) mutant. I found that charge-silencing mutagenesis within the juxtamembrane region of the EGFR generated a mutant receptor (R1-6) that spontaneously transformed NIH/3T3 mouse fibroblasts in a ligand-independent manner. Interestingly, cellular transformation occurred whether R1-6 trafficked to the plasma membrane or if it was confined to the ER. These findings highlighted the importance of the polybasic juxtamembrane sequence in regulating the oncogenic potential of EGFR signaling. Furthermore, they confirmed that wholly ER-retained, constitutively active EGFRs can drive cellular transformation. Thus, clinically, cancers mediated by similarly retained mutant EGFRs will likely be more optimally treated by inhibitors that access their intracellular location. My studies of EGFR were initially unique in my graduate laboratory, and my decision to begin this line of research spawned other projects. In one such study we investigated the spatiotemporal association of signaling proteins with EGFRs using micro-patterned EGF surfaces and observed that fluorescently labeled EGFR and tyrosine-stimulated phosphorylation were spatially confined to the patterns of immobilized EGF. We also observed the association of well-described downstream signaling partners including paxillin, phospholipase Cg, and ERK with the recruited EGFR. This was the first evidence of direct interaction of ERK with the EGFR signaling complex at the plasma membrane.

a. **Bryant KL**, Antonyak MA, Cerione RA, Baird B, Holowka D. (2013) Mutations in the polybasic juxtamembrane sequence of both plasma membrane- and endoplasmic reticulum-localized epidermal growth factor receptors confer ligand-independent cell transformation. *J Biol Chem.* 288: 34930-42. PMCID: PMC3843104
b. Singhai A, Wakefield DL, **Bryant KL**, Hammes SR, Holowka D, Baird B. (2014) Spatially defined EGF receptor activation reveals an F-actin-dependent phospho-Erk signaling complex. *Biophys. J.* 107: 2639-51. PMCID: PMC4255200

4. A specific pool of phosphatidylinositol 4-phosphate regulates protein trafficking from the endoplasmic reticulum to the plasma membrane. I also studied the role that negatively charged phospholipids, particularly phosphatidylinositol 4-phosphate (PI4P), play in biosynthetic trafficking. I developed and utilized a new protocol to characterize pharmacological inhibitors of the various isoforms of PI4-kinase that inhibit the production of PI4P at distinct organelle membranes. My findings provided evidence that a specific pool of PI4P plays a role in biosynthetic trafficking of two different classes of proteins from the ER to the plasma membrane. Furthermore,

my simple, flow cytometry-based biosynthetic trafficking assay can be widely applied to the study of multiple classes of proteins and varied pharmacological and genetic perturbations.

a. **Bryant KL**, Baird B, Holowka D. (2015) A novel fluorescence-based biosynthetic trafficking method provides pharmacological evidence that PI4-kinase IIIa is important for protein trafficking from the endoplasmic reticulum to the plasma membrane. *BMC Cell Biol*. 16:5, PMCID: PMC4355129.

A full list of publications can be found at:
https://www.ncbi.nlm.nih.gov/myncbi/1xGTtqCqRXbQq/bibliography/public/