BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Reginald Hill	Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login) RHILL2	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Florida A&M University Tallahassee, FL	B.S.	8/95-12/98	Biology
UNC Chapel Hill, Chapel Hill, NC	Ph.D.	8/99-10/05	Genetics
UCLA, Los Angeles, CA	Postdoc	10/05-8/12	Cancer Biology

A. Personal Statement

Pancreatic ductal adenocarcinoma (PDAC) has a five-year survival rate of only 9%. Late detection and remarkable chemoresistance are major factors that contribute to this dismal outcome. My lab focuses on these critical clinical needs by 1) optimizing the use of ER stress inhibition to increase chemotherapy efficacy in PDAC and 2) testing the efficacy of using CAF-derived exosomes for early detection of PDAC *in vivo.*

My laboratory has identified that increased GRP78 expression correlated with accelerated tumor development in aggressive tumors in a mouse model of PDAC (Hill et al., 2012). Furthermore, I showed for the first time that IT-139, a first-in-class ruthenium based compound capable of blocking stress-induction of GRP78, increases the efficacy of chemotherapy and leads to an increase in overall survival of mice with drug resistant tumors (Gifford et al., 2016). Our exciting findings were used as the basis of an application to the Food and Drug Administration (FDA) that successfully led to IT-139 being granted Orphan Drug Designation by the FDA for treatment as a combination therapy for PDAC patients.

In addition, my lab has shown, for the first time, that fibroblasts exposed to gemcitabine, the chemotherapeutic standard-of-care for PDAC, drastically increase the release of microvesicles called exosomes that increase chemoresistance in recipient epithelial cells (Richards et al., 2017). Our current work focuses on elucidating the molecular mechanisms through which fibroblast-derived exosomes contribute to pancreatic cancer chemoresistance. Moreover, we are expediting the use of CAF-derived exosomes to detect PDAC in patients by the construction of a microfluidic instrument that combines multiple technologies in order to isolate and lyse exosomes from biological fluids and analyze the miRNA they carry (Taller et al., 2015).

My proven history of establishing working relationships between academic researchers, industry scientists, and clinicians shows I will not hesitate to foster collaborations to test novel discoveries from my work in relevant patient samples or populations. Hence, my model systems ae ideal to test the hypothesis of this proposal.

Selected Peer-reviewed Publications (*, pancreatic cancer related)

Zeleniak A*, Huang W, Fishel M, and **Hill R**. PTEN-Dependent Stabilization of MTSS1 Inhibits Metastatic Phenotype in Pancreatic Ductal Adenocarcinoma. *Neoplasia*. 20(1):12-24. 2018. PMID: 29175021, PMC5714254.

*Zeleniak A, Huang W, Brinkman M, Fishel M, and **Hill R**. Loss of MTSS1 Results in Increased Metastatic Potential in Pancreatic Cancer. *Oncotarget 2017 Mar 7;8(10):16473-16487. doi: 10.18632/oncotarget.14869*.

*Richards, K, Zeleniak A, Fishel M, Wu J, Littlepage L, and **Hill R**. Cancer-Associated Fibroblast Exosomes Regulate Survival And Proliferation Of Pancreatic Cancer Cells. *Oncogene 2017 Mar 30;36(13):1770-1778. doi: 10.1038/onc.2016.353. Epub 2016 Sep 26.*

* Gifford J, Huang W, Zeleniak A, Hindoyan A, Wu H, Donahue T, and **Hill R**. Expression of GRP78, Master Regulator of the Unfolded Protein Response, Increases Chemoresistance in Pancreatic Ductal Adenocarcinoma. *Molecular Cancer Therapeutics* 2016 May;15(5):1043-1052. doi: 10.1158/1535-7163.
*Taller D, Richards K, Slouka Z, Senapati S, **Hill R**, Go D, and Chang H. On-Chip Surface Acoustic Wave Lysis and Ion-Exchange Nanomembrane Detection of Exosomal RNA for Pancreatic Cancer Study and Diagnosis. *Lab on a Chip* 2015 Apr 7;15(7):1656-66.)
***Hill R**, Li Y, Tran L, Garcia A, Hargan J, Kim C, Wang Y, Dry S, Donahue T, Herschman H, and Wu H. Delayed progression of pancreatic cancer development through cell-intrinsic activity of *Cox-2*. *Molecular Cancer Therapeutics* 2012 July 12.
*Donahue T, Tran L, **Hill R**, Li Y, Kovochich, Calvopina J, Patel S, Hindoyan A, Farrell J, Li X, Dawson D, and Wu H. An Integrative Survival-Based Genomic and Molecular Profile of Human Pancreatic Cancer. *Clinical Cancer Research.* 2012 Mar 1;18(5):1352-63)
***Hill R**, Hargan J, Kim C, Wang Y, Dawson D, Donahue T, Dry S, and Wu H. PTEN Loss Accelerates KrasG12D-Induced Pancreatic Cancer Development. *Cancer Research*. 2010 Sep 15;70(*18*):7114-24.

B. Positions and Honors

08/1999 – 10/2005 Graduate Student, Genetics Department, UNC Chapel Hill, Chapel Hill, NC
10/2005 – 08/2012 Postdoctoral Fellow, Molecular and Medical Pharmacology Department, UCLA, Los Angeles, California
08/2012 – 08/2018 Assistant Professor, Department of Biological Sciences, University of Notre Dame, South Bend, Indiana
08/2018 – Present Assistant Professor, Department of Medicine, University of Southern California, Los Angeles, California

Honors

1999 Research Education Support Summer Program Fellow (RES) (UNC-CH)
2001 GEM Fellow (UNC-CH)
2003 Graduate Mentor Support Grant (UNC-CH)
2004 AACR Minority Scholar Award
2006 UNCF/Merck Postdoctoral Science Research Fellowship -Declined
2006-2009 Damon Runyon Cancer Research Foundation Fellowship
2009-2011 UCLA Tumor Cell Biology Fellowship Award (T32)
2012 Endowment (Archibald Assistant Professor of Cancer Biology)

C. Contributions to science

Uncoupling the contributions of the RB family, PTEN, and p53 in prostate tumorigenesis.
I designed and created a new transgenic mouse model of prostate cancer based on retinoblastoma gene *(RB)* family inactivation. I discovered that complete pRb family inactivation caused the development of severe prostate cancer. This indicated that functional redundancy or compensation in prostate epithelium by pRb family members p107 and p130 also played a critical role in suppression of prostate tumor formation. I was interested in understanding how multiple genetic alterations contributed to tumor progression, so I next examined how inactivation of two frequently mutated tumor suppressors in prostate cancer, *p53* and *Pten*, further promoted tumor progression after RB inactivation. I found that selective pressure for *Pten* LOH accelerated tumor progression and enhanced tumor survival. Interestingly, I uncovered that tumor initiation due to pRb family inactivation in the epithelium created selective pressure for *p53* loss in the surrounding stromal cells, identifying a critical role for p53 in the mesenchyme. Most importantly, this stromal alteration aided further tumor progression. This work represented the first *in vivo* model of spontaneous tumor progression where selective mutation in the reactive stroma was identified as a mechanism for neoplastic acceleration. This underscored the importance of the microenvironment in tumor progression and supported the emerging concept of targeting the tumor microenvironment as a valid therapeutic strategy.

Hill R, Song Y, Cardiff R, and Van Dyke T. Selective evolution of stromal mesenchyme with p53 loss in response to epithelial tumorigenesis. *Cell*. 2005 Dec 16;123(*6*):1001-11.

Hill R, Song Y, Cardiff R, and Van Dyke T. Heterogeneous tumor evolution initiated by loss of pRb function in a preclinical prostate cancer model. *Cancer Research*. 2005 Nov 15;65(*22*):10243-54.

Elucidating mechanisms through which PTEN and COX-2 controlled signaling pathways contribute to pancreatic cancer initiation, progression, and chemoresistance.

I chose to focus on an area of research with a largely unmet need for translational research. Pancreatic cancer (PDAC) has a high mortality rate, dismal prognosis and few therapeutic options. This points to a dire need for novel therapeutic and chemopreventative strategies, and for relevant research models of disease development. I played a central role in establishing a translational research team to develop mouse models that best recapitulated human PDAC and translated these findings to the human disease. The most commonly observed genetic alterations in PDAC are constitutively activating mutations in *KRAS*. Aberrant activation of the PI3K/AKT pathway by either PTEN loss or other mechanisms had been observed in a significant subset of human PDACs, yet PTEN's role in tumor progression had yet to be determined. I decided to investigate this and found that concomitant loss of *Pten* with expression of a constitutively active $Kras^{G12D}$ mutant allele drastically accelerated tumor development, and increased the number of cells possessing the hallmarks of cancer stem/therapy resistant cells. This indicated that PI3K/AKT and KRAS signaling pathways act synergistically to promote pancreatic initiation and progression and moreover, established PTEN as the gatekeeper to tumorigenesis in the pancreas. Recognizing that inflammation is a predisposing risk for cancer development, I next chose to directly test the role inflammation plays in pancreatic tumorigenesis. COX-2, a key mediator of inflammation, is up-regulated in all stages of PDAC development and portends a poor prognosis for patients. However, its role in tumor development has yet to be fully investigated. I developed a novel mouse model of PDAC, based on COX-2 over-expression, which fully recapitulates the severe inflammatory response observed in the human disease, an important feature missing in previously developed models. I identified cell intrinsic mechanisms through which COX-2 expression can lead to accelerated tumor progression and most importantly, resistance to current treatment regimens by activation of signaling pathways linked to cell survival.

Hill R and Wu H. PTEN, Stem Cells, and Cancer Stem Cells. *Journal of Biological Chemistry*. 2009 May 1;284(*18*):11755-9.

Hill R, Li Y, Tran L, Garcia A, Hargan J, Kim C, Wang Y, Dry S, Donahue T, Herschman H, and Wu H. Delayed progression of pancreatic cancer development through cell-intrinsic activity of *Cox-2*. *Molecular Cancer Therapeutics* 2012 Oct; 11(10): 2127–2137.

Hill R, Hargan J, Kim C, Wang Y, Dawson D, Donahue T, Dry S, and Wu H. PTEN Loss Accelerates KrasG12D-Induced Pancreatic Cancer Development. *Cancer Research*. 2010 Sep 15;70(*18*):7114-24.

Identification of molecular mechanisms that contribute to poor prognosis in PDAC.

My previous studies indicated that PI3K/AKT and KRAS signaling pathways act synergistically to promote pancreatic initiation and progression and moreover, established PTEN as the gatekeeper to tumorigenesis in the pancreas. To extend my findings to the human disease, I designed a global microarray analysis project with a surgeon-scientist at UCLA to obtain human pancreatic cancer samples for validation that mechanisms of disease progression observed in my mouse models were mirrored in the human disease. We were able to show that PI3K/AKT pathway activation is strongly linked to clinical disease progression, a finding that may dictate the variable response to targeted therapy seen in the PDAC patient population. Moreover, I initiated another project that integrated data from array data from mouse models of pancreatic cancer with human patient array data to identify novel genes that can cause chemoresistance that will aid the development of more effective treatment strategies.

Donahue T, Tran L, **Hill R**, Li Y, Kovochich, Calvopina J, Patel S, Hindoyan A, Farrell J, Li X, Dawson D, and Wu H. An Integrative Survival-Based Genomic and Molecular Profile of Human Pancreatic Cancer. *Clinical Cancer Research.* 2012 Mar 1;18(5):1352-63)

Microfluidic-based Identification of Exosomal miRs for Early Detection of Pancreatic Cancer.

Early detection of pancreatic cancer is critical to improve overall survival rates. A number of recent findings have suggested that understanding miRNA regulation and expression is essential to understanding cancer development and improving cancer detection, prevention, and therapeutic strategies. More importantly, due to their short sequence length, which leads to increased stability, miRNAs are ideal circulating biomarkers.

Pancreatic cancer cells can communicate with each other, or cells of the surrounding microenvironment, via miRNA. The miRNA transfer between cells in the tumor is mediated by exosomes, secreted membrane vesicles that range in size from 40–100 nm in diameter. Therefore, collection of circulating miRNAs—enclosed in exosomes/vesicles—may prove to have great potential as biomarkers for many cancers, including pancreatic cancer. However, extracting vesicles from extracellular biological matrices is not trivial. It typically requires multiple stages of ultra-centrifugation or field-flow fractionation to isolate them, and the yield is very low as many exosomes are lost during the separation process. I initiated a collaborative project where we developed microfluidics-based technologies that can be used for the rapid separation and analysis of exosomes essential in studying the role of miRNAs in pancreatic cancer initiation, progression, and chemoresistance. This research was conducted in two phases. First, a SAW-based microfluidic separation device was developed and fabricated and tested on spherical nanoparticles of ~100 nm diameter. After basic characterization of the separation efficiency, the device was used on vesicle isolated from patient-derived samples and biological fluids from pancreatic cancer animal models to test the diagnostic ability of our device. At a total analysis time of ~1.5 h, this approach is a significant improvement over existing methods that require two overnight steps and 13 h of processing time. The platform also requires much smaller sample volumes than existing technology (~100 µL as opposed to ~mL) and operates with minimal sample loss, a distinct advantage for studies involving mouse models or other situations where the working fluid is scarce.

Taller D, Richards K, Slouka Z, Senapati S, **Hill R**, Go D, and Chang H. On-Chip Surface Acoustic Wave Lysis and Ion-Exchange Nanomembrane Detection of Exosomal RNA for Pancreatic Cancer Study and Diagnosis. *Lab on a Chip* 2015 Apr 7;15(7):1656-66).

Investigation of how stromal cell-derived exosomes mediate chemoresistance in pancreatic cancer.
Cancer associated fibroblasts (CAFs) comprise the majority of the tumor bulk of pancreatic adenocarcinomas (PDACs). Current efforts to eradicate these tumors focus predominantly on targeting the proliferation of rapidly growing cancer epithelial cells. We know that this is largely ineffective with resistance arising in most tumors following exposure to chemotherapy. Despite the long-standing recognition of the prominence of CAFs in PDAC, the effect of chemotherapy on CAFs and how they may contribute to drug resistance in neighboring cancer cells is not well characterized. Here we show that CAFs exposed to chemotherapy play an active role in regulating the survival and proliferation of cancer cells. We found that CAFs are intrinsically resistant to gemcitabine, the chemotherapeutic standard of care for PDAC. Further, CAFs exposed to gemcitabine significantly increase the release of extracellular vesicles called exosomes. These exosomes increased chemoresistance-inducing factor, *SNAIL*, in recipient epithelial cells and promote proliferation and drug resistance. Finally, treatment of gemcitabine-exposed CAFs with an inhibitor of exosome release, GW4869, significantly reduces survival in co-cultured epithelial cells, signifying an important role of CAF exosomes in chemotherapeutic drug resistance. Collectively, these findings show the potential for exosome inhibitors as treatment options alongside chemotherapy for overcoming PDAC chemoresistance.

Richards, K, Zeleniak A, Fishel M, Wu J, Littlepage L, and **Hill R**. Cancer-Associated Fibroblast Exosomes Regulate Survival And Proliferation Of Pancreatic Cancer Cells. *Oncogene 2017 Mar 30;36(13):1770-1778. doi: 10.1038/onc.2016.353. Epub 2016 Sep 26.*

Elucidation of the role of the ER stress response in the chemoresistance of pancreatic cancer.
Endoplasmic Reticulum (ER) stress response proteins are produced by cells undergoing periods of stress and facilitate the folding of proteins. Interestingly, ER stress response proteins are also overexpressed in cancer cells, and are often associated with high resistance to chemotherapy and poor prognosis. Our data show that drug resistant PDACs are under constant ER stress, most likely due to the increased inflammatory response that is a major hallmark of PDAC. Our results show that the increased expression of GRP78, the master regulator of the ER stress response, is critical for chemoresistance in PDAC. I have shown that knockdown of GRP78 increases chemotherapy sensitivity in PDAC. Moreover, we found that an inhibitor of GRP78, IT-139, can overcome GRP78 mediated chemoresistance. Collectively, our data show that GRP78 expression promotes chemoresistance in PDAC and therapeutic strategies blocking the activity of GRP78 increase the efficacy of currently available therapies.

Gifford J, Huang W, Zeleniak A, Hindoyan A, Wu H, Donahue T, and **Hill R**. Expression of GRP78, Master Regulator of the Unfolded Protein Response, Increases Chemoresistance in Pancreatic Ductal Adenocarcinoma. *Molecular Cancer Therapeutics* 2016 May;15(5):1043-1052.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/47626289/

D. Research Support

Completed Research Support

R21 (09/01/2016-8/31/2018)
National Institutes of Health (PAR-13-303)
1 R21 HG009010-01A1
"An Integrated Microfluidics Platform for Rapid and Sensitive Exosome RNA"
Role: Co-Principal Investigator: Reginald Hill
Major Goals: The main goal of this project is to develop a microfluidics platform that can rapidly separate and isolate exosomes and detect and identify the microRNA and messenger RNA they carry. The projected speed and sensitivity of this device will enable the rapid and early detection of exosomal RNA that are diagnostic or prognostic biomarkers for pancreatic cancer.

American Cancer Society 1/1/17-12/31/17
ACS Pilot Research Grant - Institutional Research Grant #IRG-14-195-01
"Investigation Of Stromal-Derived Exosomes In The Chemoresistance Of Pancreatic Cancer"
Role: Principal Investigator: Reginald Hill
Major Goals: We will determine the clinical significance of targeting exosomal-mediated chemoresistance *in vivo* by blocking exosome release. These results will give us knowledge that is clinically relevant and can be applied to any disease or molecular target stimulated by exosome signaling.

Intezyne Sponsored Research Grant (8/1/16-8/31/17)
"Utilizing IT-139 To Sensitize Drug Resistant PDAC Cells To Currently Available Therapeutic Regimens"
Role: Principal Investigator: Reginald Hill
Major Goals: We aim to evaluate combination treatment benefits of gemcitabine, the current chemotherapeutic standard, with IT-139 in PDAC cells lines.

Walther Cancer Foundation (8/1/14-8/1/15)
Seeding Research in Cancer Grant (SRC)
"Utilizing ER Stress Inhibition to Sensitize Drug Resistant Pancreatic Cancer to Gemcitabine Treatment"
Role: Principal Investigator: Reginald Hill
Major Goals: We propose to increase the efficacy of gemcitabine in treating pancreatic cancer by reducing the expression of the "pro-survival", stress-induced molecular chaperone, GRP78. We will evaluate the effect of GRP78 inhibition on the chemoresistance of pancreatic cancer cells by inhibiting GRP78 expression using siRNA directed against GRP78 that decrease GRP78 expression.

Indiana CTSI Core Pilot Proposal (9/1/13-8/31/15)
Indiana Clinical and Translational Sciences Institute (Funded by NIH,NCATS, CTSA)
"Identifying Stromal MicroRNAs Mediating Chemoresistance in Pancreatic Cancer."
Role: Principal Investigator: Reginald Hill
Major Goals: In this proposal we plan to generate a PDAC stromal miRNA signature in both drug sensitive and drug resistant PDAC stromal cells. By functionally isolating stromal cells from drug sensitive and drug resistant tumors, we will be able to identify stromal miRNA profiles which will allow us to address the hypothesis that PDAC chemoresistance is largely mediated by stromal cells by a definable set of miRNAs.