BIOGRAPHICAL SKETCH

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NAME: Capell, Brian Curran

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POSITION TITLE: Assistant Professor of Dermatology and Genetics

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
Boston College, Chestnut Hill, MA	B.S.	05/2000	Biology
Howard Hughes Medical Institute – National Institutes of Health Research Scholars Program		2004-2006	Genetics
New York University School of Medicine, New York, NY	Ph.D.	05/2008	Cellular and Molecular Biology
New York University School of Medicine, New York, NY	M.D.	05/2009	Medicine
Pennsylvania Hospital, Philadelphia, PA		06/2010	Medicine Internship
Hospital of the University of Pennsylvania, Philadelphia, PA	Board Certified	06/2013	Dermatology Residency
University of Pennsylvania Perelman School of Medicine, Philadelphia, PA	Postdoctoral Fellowship	2013-17	Epigenetics

A. Personal Statement

I am a board-certified practicing dermatologist and currently an Assistant Professor of Dermatology and Genetics, core faculty member of the Penn Epigenetics Institute, and member of Penn Institute for Regenerative Medicine and the Abramson Cancer Center at the University of Pennsylvania Perelman School of Medicine. Fascinated by the emerging field of epigenetics and gene regulation, following the completion of my clinical dermatology residency, I pursued advanced postdoctoral training under the mentorship of Dr. Shelley Berger, a pioneer in the field of epigenetics. Through these experiences, I have gained a unique combination of basic and translational research expertise in the interrogation of epigenetic and gene regulatory mechanisms in epithelial and cancer biology. My independent research program is focused on answering fundamental questions regarding the role of the epigenome and epitranscriptome in epithelial cancers. Building off of my previous experiences working on aging and senescence during my Ph.D. with Dr. Francis Collins, combined with my postdoctoral work studying chromatin regulatory enzymes in aging and cancer, my laboratory is ideally suited to define the links between gene regulatory dysfunction and epithelial development, differentiation, regeneration and carcinogenesis. I have assembled a talented and vibrant team of graduate students, postdoctoral fellows, and bioinformatics specialists to work in conjunction with our expert collaborators in achieving these goals. I anticipate that the concepts gleaned from our studies combining human patient samples, 3D organotypic human skin models, primary epithelial cells, and novel transgenic mouse models with cutting-edge technological approaches will identify new targets for prevention and treatment disorders of stratifying epithelia such as the skin. Our recently published work has identified a new connection between the emerging form of programmed cell death known as ferroptosis, and the balance between epidermal differentiation and cancer. Given the inherent targetability of epigenetic regulators, these

studies hold promise to help identify new therapeutic approaches for diseases of epithelial tissues such as the skin.

Ongoing and recently completed projects that I would like to highlight include:

R01 AR077615
Capell (PI)
07/15/20-06/30/25
Epigenetic enhancer control in maintaining homeostasis and preventing carcinogenesis in the epidermis

Dermatology Foundation Charles and Daneen Stiefel Award
Capell (PI)
07/01/19-06/30/22
Restoring epigenomic histone methylation dynamics for the treatment of keratinocyte carcinomas

Damon Runyon Clinical Investigator Award
Capell (PI)
07/01/18-06/30/21
Defining the role of epigenetic enhancer dysfunction in epithelial carcinogenesis

K08 AR070289
Capell (PI)
07/20/16-06/30/21
Epigenomic Mechanisms of Skin Carcinogenesis

Citations:

1. Egolf S, Zou J, Anderson A, Simpson CL, Aubert Y, Prouty S, Ge K, Seykora JT, **Capell BC**. MLL4 mediates differentiation and tumor suppression through ferroptosis. Sci Adv. 2021 Dec 10;7(50):eabj9141. doi: 10.1126/sciadv.abj9141. Epub 2021 Dec 10. PMID: 34890228; PMCID: PMC8664260.

2. Egolf S, Aubert Y, Doepner M, Anderson A, Maldonado-Lopez A, Pacella G, Lee J, Ko EK, Zou J, Lan Y, Simpson CL, Ridky T, **Capell BC**. LSD1 Inhibition Promotes Epithelial Differentiation through Derepression of Fate-Determining Transcription Factors. Cell Rep. 2019 Aug 20;28(8):1981-1992.e7. doi: 10.1016/j.celrep.2019.07.058. PMID: 31433976; PMCID: PMC6719800.

3. Lin-Shiao E, Lan Y, Coradin M, Anderson A, Donahue G, Simpson CL, Sen P, Saffie R, Busino L, Garcia BA, Berger SL, **Capell BC**. "KMT2D regulates p63 target enhancers to coordinate epithelial homeostasis." *Genes Dev*.32(2): 2018. PMID: 29440247

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022-present Admissions Committee, Penn Medical Scientist Training Program (MSTP)
2022-present Tumor Biology Program Liasion, Community Outreach and Engagement (COE) at the Abramson Cancer Center (ACC)
2022-present Ad hoc reviewer, *Nature Communications, Frontiers in Cell and Developmental Biology*
2021-present Faculty mentor and advisor, Trainee Advocacy Alliance of the Penn Office of Research & Diversity Training
2020-present Ad hoc reviewer, *New England Journal of Medicine, Nature Genetics*
2020-present Associate Editor, *Frontiers in Oncology*
2020-present Co-Core Director, Cutaneous Phenomics and Transcriptomics (CPAT) Core, NIH P30 Penn Skin Biology and Disease Research Center

2020-present Steering Committee, Richards Society, University of Pennsylvania
2019-present Professionalism Committee, Department of Dermatology, University of Pennsylvania
2019-2024 Society of Investigative Dermatology Committee on Education
2019-present Ad hoc reviewer, *Cellular and Molecular Life Sciences*, *Epigenetics*, *Yale Journal of Biology and Medicine*
2018-present Ad hoc reviewer, *Nature Biotechnology*, *Cell Reports*, *PNAS*, *British Journal of Dermatology*, *JAMA Dermatology*
2017-present Ad hoc reviewer, *Cell Stem Cell*, *Aging Cell*
2017-present Assistant Professor of Dermatology and Genetics, Penn Epigenetics Institute, Penn Institute for Regenerative Medicine, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA
October 2018 Ad hoc member, Arthritis, Connective Tissue, and Skin (ACTS) Study Section, NIAMS, NIH
2014-present Leaders Society, Dermatology Foundation
2013-present Ad hoc reviewer, *Journal of Investigative Dermatology*
2013-17 Instructor and Postdoctoral Fellow, Dermatology Department and Epigenetics Institute, University of Pennsylvania, Philadelphia, PA (Mentor: Shelley Berger, Ph.D.)
2010-13 Resident in Dermatology, Hospital of the University of Pennsylvania, Philadelphia, PA
2010-present Member, Society of Investigative Dermatology
2010-present Member, American Academy of Dermatology
2009-10 Preliminary Intern in Internal Medicine, Pennsylvania Hospital, Philadelphia, PA
2004-08 HHMI-NIH Research Scholar, MSTP Student, National Human Genome Research Institute, NIH, Bethesda, MD (Mentor: Francis Collins, M.D., Ph.D.)

Honors

2019 Dermatology Foundation Charles and Daneen Steifel Award for Skin Cancer
2018 Young Investigator of the Year Award, American Academy of Dermatology
2018 Young Physician-Scientist Award, American Society for Clinical Investigation
2018 Damon Runyon Clinical Investigator Award, Damon Runyon Cancer Foundation
2014 Albert Kligman Fellowship, Society of Investigative Dermatology
2008 William Randolph Hearst Foundation Fellow, NYU MSTP Award
2007 57th Meeting of Nobel Laureates in Physiology and Medicine, Lindau, Germany, July 2007, selected as one of 50 students to the U.S. delegation
2007 International Achievement Summit of the Academy of Achievement, Washington, DC, June 2007, selected student attendee
2006 National Institutes of Health Intramural Research Training Award (NHGRI)
2006 American Society of Human Genetics, Predoctoral Award First Place Winner, 56th Annual Meeting, New Orleans, Louisiana, October 2006
2005 Howard Hughes Medical Institute Continuing Support Award
2004 Howard Hughes Medical Institute-NIH Research Scholars Program Fellowship
2000 Magna Cum Laude and Alpha Sigma Nu National Honor Society, Boston College

C. Contributions to Science

1. *Demonstrated the first role for ferroptosis in epidermal differentiation and tumor suppression:* Our recent studies have uncovered a potential link between the emerging form of programmed cell death known as ferroptosis and the execution of both epidermal differentiation and tumor suppression in the skin. Beyond identifying the mechanisms through which MLL4 (KMT2D) promotes differentiation and exerts its tumor suppressive functions, these studies have revealed evidence that ferroptosis may be the essential mechanism by which keratinocytes ultimately die and form the cornified envelope of the epidermal barrier. Given that numerous skin disorders are driven by dysregulated epidermal differentiation, combined with the ability to both pharmacologically induce and inhibit ferroptosis, these studies have provided proof of principal that ferroptosis modulation may a viable therapeutic strategy for a variety of skin disorders.

a. Egolf S, Zou J, Anderson A, Simpson CL, Aubert Y, Prouty S, Ge K, Seykora JT, **Capell BC**. MLL4 mediates differentiation and tumor suppression through ferroptosis. Sci Adv. 2021 Dec

10;7(50):eabj9141. doi: 10.1126/sciadv.abj9141. Epub 2021 Dec 10. PMID: 34890228; PMCID: PMC8664260.

2. *Elucidated the importance of the KMT2D-LSD1-H3K4 methylation axis in epithelial homeostasis:* Epithelial tissues rely on a highly coordinated balance between self-renewal, proliferation and differentiation; disruption of which may drive carcinogenesis. Here we established the first known role of the epigenetic regulator *KMT2D* (*MLL4*) in epithelial enhancer control, including the regulation of p63-target genes involved in epithelial development, differentiation and stratification. Additionally, we have now shown that LSD1 serves to oppose the role of KMT2D by repressing major fate-determining transcription factors that drive epithelial differentiation and may serve as an effective therapeutic target for cutaneous squamous cell carcinoma.

a. Lin-Shiao E, Lan Y, Coradin M, Anderson A, Donahue G, Simpson CL, Sen P, Saffie R, Busino L, Garcia BA, Berger SL, **Capell BC**. "KMT2D regulates p63 target enhancers to coordinate epithelial homeostasis." *Genes Dev*.32(2): 2018. PMID: 29440247
b. Egolf S, Aubert Y, Doepner M, Anderson A, Maldonado-Lopez A, Pacella G, Lan Y, Simpson CL, Ridky T, **Capell BC**. "LSD1 inhibition promotes epithelial differentiation through derepression of fate-determining transcription factors." *Cell Reports*. 28(8): 2019. PMID: 31433976
c. Aubert Y, Egolf S, **Capell BC**. "The Unexpected Noncatalytic Roles of Histone Modifiers in Development and Disease." *Trends in Genetics*. 35(9): 2019. PMID: 31301850
d. Egolf S, **Capell BC**. "LSD1: a viable therapeutic target in cutaneous squamous cell carcinoma?" *Expert Opin Ther Targets*. Online ahead of print: 2020. PMID: 32379508

3. *Demonstrated the role of MLL1 and chromatin alterations in senescence and DNA damage-induced inflammation:* We have shown that senescent cells possess large-scale alterations in the epigenome (Shah, et al. 2013; Dou, et al. 2015), and that MLL1, a known H3K4me3 methyltransferase and oncogene, is critical for the expression of DNA-damage response (DDR)-induced inflammation (Capell, et al. 2016), also known as the senescence-associated secretory phenotype (SASP) in the context of senescence (Ghosh and Capell, et al. 2016). MLL1 inhibition can dramatically attenuate the expression and secretion of the SASP, and ameliorate the pro-carcinogenic effects of the SASP, while having no effects on the expression of tumor suppressors or the senescence growth arrest. Together this work suggests that epigenetic abnormalities in senescence can be targeted to prevent its pro-cancer and pro-aging effects.

a. Shah PP, Donahue G, Otte G, **Capell BC**, Nelson DM, Cao K, Aggarwala V, Cruickshanks HA, Singh Rai T, McBryan T, Gregory BD, Adams PD, Berger SL. "Lamin B1 depletion in senescent cells triggers large-scale changes in gene expression and in the chromatin landscape" *Genes Dev*. 27(16): 2013. PMID: 23934658
b. Dou Z, Xu C, Donahue G, Ivanov A, Pan J, Zhu J, **Capell BC**, Catanzaro JM, Ricketts MD, Shimi T, Adam SA, Mamorstein R, Zong WX, Goldman RD, Johansen T, Adams PD, Berger SL. "Autophagy mediates degradation of nuclear lamina." *Nature*. 527(7576): 2015. PMID: 26524528
c. **Capell BC**, Drake AM, Zhu J, Shah PP, Dou Z, Dorsey J, Simola DF, Donahue G, Sammons M, Rai TS, Natale C, Ridky TW, Adams PD, Berger SL. MLL1 is essential for the senescence-associated secretory phenotype. Genes Dev. 2016 Feb 1;30(3):321-36. doi: 10.1101/gad.271882.115. PMID: 26833731; PMCID: PMC4743061.
d. Dou Z, Ghosh K, Vizioli MG, Zhu J, Sen P, Wangensteen KJ, Simithy J, Lan Y, Lin Y, Zhou Z, **Capell BC**, Xu C, Xu M, Kieckhaefer JE, Jiang T, Shoshkes-Carmel M, Tanim KM, Barber G, Seykora JT, Millar SE, Kaestner KH, Garcia BA, Adams PD, Berger SL. "Cytoplasmic chromatin triggers inflammation in senescence and cancer". *Nature*. 550(7676): 2017. PMID: 28976970

4. *Established farnesyltransferase inhibitors as a potential therapy for Hutchinson-Gilford progeria syndrome (HGPS):* We have demonstrated both *in vitro* and *in vivo* that farnesyltransferase inhibitors (FTIs) are efficacious in improving phenotypes in model systems of the most dramatic form of human premature aging, HGPS. This work was proof of principle that FTIs may be effective for the cardiovascular disease which is the major cause of mortality in HGPS. This work has been replicated by numerous other labs, and FTIs have now been shown to improve patient phenotypes in the very first clinical trial of human HGPS patients. The FTI, lonafarnib, is now FDA-approved and is currently the standard of care for this rare but deadly disease.

a. **Capell BC**, Erdos MR, Madigan JP, Fiordalisi JJ, Varga R, Conneely KN, Gordon LB, Der CJ, Cox AD, Collins FS. “Inhibiting the farnesylation of progerin prevents the characteristic nuclear blebbing of Hutchinson-Gilford progeria syndrome”. *Proc Natl Acad Sci USA.* 102(36): 2005. PMID: 16129833
b. Varga R, Eriksson M, Erdos MR, Olive M, Harten I, Kolodgie F, **Capell BC**, Cheng J, Faddah D, Perkins S, Avallone H, San H, Qu X, Ganesh S, Gordon LB, Virmani R, Wight TN, Nabel EG, Collins FS. “Progressive vascular smooth muscle cell defects in a mouse model of Hutchinson-Gilford progeria syndrome”. *Proc Natl Acad Sci USA.* 103(9): 2006. PMID: 16492728
c. “Farnesyltransferase inhibitors for treatment of laminopathies, cellular aging and atherosclerosis.” Filed with the United States Patent and Trademark Office, European Patent Office, international patent number: 06733984.6-2123-US2006002977 (USPTO#: 20080131375 - Class: 424 92 USPTO). Publication Number: WO/2006/081444 with the World Intellectual Property Organization: 2007.
d. **Capell BC**, Olive M, Erdos MR, Cao K, Faddah DA, Whipperman M, San H, Qu X, Ganesh SK, Chen X, Avallone H, Kolodgie F, Virmani R, Nabel EG, Collins FS. “A farnesyltransferase inhibitor prevents the onset and late progression of cardiovascular disease in a progeria mouse model”. *Proc Natl Acad Sci USA.* 105(41): 2008. PMID: 18838683

5. *Demonstrated links between mechanisms of premature aging in Hutchinson-Gilford progeria syndrome (HGPS) and the normal human aging process:* We have shown that in normal human aging, cells also produce small but increasing amounts of the mutant protein, progerin, which directly causes premature aging in HGPS. These increases in progerin lead to abnormalities in nuclear architecture with aging in both HGPS and normal cells. Furthermore, we have demonstrated that variations in the *LMNA* gene, which when mutated can cause HGPS as well as other diseases of premature aging, may in fact serve a protective function, as a particular form (haplotype) of this gene was overrepresented in centenarian populations.

a. Cao K, **Capell BC**, Erdos MR, Djabali K, Collins FS. “A lamin A protein isoform overexpressed in Hutchinson-Gilford progeria syndrome interferes with mitosis in both progeria and normal cells”. *Proc Natl Acad Sci USA.* 104(12): 2007. PMID: 17360355
b. **Capell BC**, Collins FS. “Human laminopathies: nuclei gone genetically awry”. *Nat Rev Genet*. 7(12): 2006. PMID: 17139325
c. **Capell BC**, Tlougan BE, Orlow SJ. “From the rarest to the most common: insights from progeroid syndromes into skin cancer and aging.” *J Invest Dermatol*. 129(10): 2009. PMID: 19387478
d. Conneely KN, **Capell BC**, Erdos MR, Sebastiani P, Timofeev N, Terry DF, Baldwin CT, Budagov T, Atzmon G, Barzalai N, Thomas GA, Puca AA, Perls TT, Geesaman BJ, Boehnke M, Collins FS. “Human longevity and common variations in the *LMNA* gene: a meta-analysis.” *Aging Cell.* 11(3): 2012. PMID: 22340368

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1-Yr5_bbnRkAY/bibliography/public/