BIOGRAPHICAL SKETCH

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NAME: **William Y. Kim, MD**

eRA COMMONS USER NAME: WILLIAM_KIM

POSITION TITLE: Associate Professor of Medicine and Genetics

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Wesleyan University, Middletown, CT	B.A.	05/1992	Economics/Biology
Brown University School of Medicine, Providence, RI	M.D.	05/1996	Medicine
Beth Israel Hospital, Boston, MA	Resident	1996-1999	Internal Medicine
Dana-Farber Cancer Institute, Boston, MA	Fellow	1999-2002	Hematology/Oncology
Dana-Farber Cancer Institute, Boston, MA	Post-doc	2000-2005	Cancer Biology

A. Personal Statement

Dr. Kim is a laboratory based physician-scientist. The Kim Laboratory studies the genetics and cancer biology underlying bladder cancer initiation and progression. The Kim Lab uses in vitro methods as well as both patient derived xenograft tumors and genetically engineered murine models of cancer (GEMMs). Dr. Kim has generated a number of novel knock-in strains himself (Kim et al, *EMBO J,* 2006) as well as been intimately involved in generating novel GEM models, such as a recent report of the first clear cell ovarian cancer GEM model (Chandler et al, *Nat Comm,* 2014) and papillary and clear cell kidney cancer GEMs (Bailey et al, *Nat Comm*, 2017. *In press*). In recognition of Dr. Kim's expertise in mouse models of cancer, he was recently appointed Co-Director of UNC's Mouse Phase 1 Unit (MP1U) alongside Dr. Chuck Perou. The Kim Lab is particularly interested in the genomics and tumor biology underlying bladder cancer and renal cell carcinoma (RCC) and strive to generate genomic observations from primary tumors and investigate their function in vitro and in vivo. Finally, Dr. Kim is involved in the NextGen sequencing of both human and mouse cancer genomes as the Chair of the Clinical Committee for Genomic Research (CCGR) for the Lineberger's UNCseq™ clinical sequencing initiative as well as the Director for Genomic Research for UNC's Mouse Phase 1 Unit (MP1U) respectively. Clinically, Dr. Kim takes care of patients with kidney and bladder cancer and is the Director of the VHL Comprehensive Clinical Care Center at UNC.

B. Positions and Honors

Professional Positions:

2002-2005 Instructor in Medicine, Harvard Medical School, Boston, MA
2002-2005 Attending Physician, Brigham and Women's Hospital, Boston, MA
2002-2005 Attending Physician, Dana-Farber Cancer Institute, Boston, MA
2005-2007 Instructor in Medicine, University of North Carolina, Chapel Hill, NC
2007-2013 Assistant Professor of Medicine, University of North Carolina, Chapel Hill, NC
2009-2012 Associate Editor, Journal of Cellular and Molecular Medicine
2009-2013 Assistant Professor of Genetics, University of North Carolina, Chapel Hill, NC
2013-present Associate Professor of Medicine and Genetics, University of North Carolina, Chapel Hill, NC
2013-present Director, Genomic Research, UNC Mouse Phase 1 Unit
2013-present Chair, Clinical Committee on Genomic Research, UNCseq™
2015-present Co-Director, UNC Mouse Phase 1 Unit
2015-present Director, VHL Comprehensive Clinical Care Center
2015-present Member, Genetics and Molecular Biology Curriculum Executive Committee
2015-present Editorial Board, *Bladder Cancer*
2015-present Consultant Editor, *JCI Insight*
2016-present Associate Director for Research, UNC Hematology/Oncology Fellowship Program

Honors:

1991 Howard Hughes Research Fellowship in Life Sciences, Wesleyan University
1992 Cum Laude, Wesleyan University
1992 White Prize in Economics, Wesleyan University
2002 American Society of Clinical Oncology Young Investigator Award
2003 Harvard Medical School, Scholars in Medicine Award
2003 AstraZeneca Young Investigator Award
2004 SPORE Renal Cell Carcinoma, Career Development Award
2004 NIH F32 (CA108314) Kirschstein NRSA Individual Fellowship (declined)
2004 NIH K08 (CA097203) Physician – Scientist Training Award
2008 DOD Prostate Cancer New Investigator Award
2008 Melanoma Research Foundation, Career Development Award
2009 Damon Runyon Clinical Investigator Award
2010 DOD Prostate Cancer Physician Research Training Award
2010 University Cancer Research Fund, Innovation Award
2012 AACR, Kure It, Grant for Kidney Cancer Research
2014 Elected member, the American Society of Clinical Investigation (ASCI)
2014 Bladder Cancer Advocacy Network (BCAN) Innovation Award
2015 Rush S. Dickson Distinguished Associate Professor of Medicine

C. Contributions to Science

The role of the von Hippel-Lindau tumor suppressor gene and the hypoxia-inducible factor family of transcription factors to solid tumorigenesis.

The majority of cancers have inactivation of the von Hippel-Lindau (VHL) tumor suppressor gene. Dr. Kim's early work consisted of defining the role of VHL inactivation in renal cell carcinoma (RCC). In particular Dr. Kim's work consisted of investigating the mechanism of tumor suppression by the VHL gene product, pVHL. During his post-doctoral fellowship with Dr. William Kaelin, Jr. he produced in vivo data that the phenotypes induced by VHL loss were copied by activation of the hypoxia-inducible factor (HIF) transcription factor through generation of Cre inducible strains of stabilized HIF1 and HIF2 mice (1). To better understand the role of HIF in solid tumors Dr. Kim, in his own lab, then crossed the inducible HIF2 mice to a KRas-driven genetically engineered mouse model (GEMM) of lung cancer. This work published in *JCI* demonstrated that HIF2α promotes angiogenesis, invasion and metastases as well as induces squamous differentiation in a KRas-driven genetically engineered mouse model of lung cancer (2). These data were the first in vivo evidence, in autochthonous tumors, that HIF can induce EMT and established HIF2α as a promoter of tumor progression in a cancer other than renal cell carcinoma. Further exploration of the roles of HIF1 and HIF2 in melanoma demonstrated that inactivation of HIF1α or HIF2α are essential for metastases in a *Pten; Braf* mutant genetically engineered mouse model of melanoma (3). Specifically, HIF1α and HIF2α activate distinct transcriptional programs to activate SRC as well as degrade the extracellular matrix, promoting melanoma invasion and metastases. The work provides the first report that HIF is necessary and sufficient for invadopodia formation and demonstrates that the potent prometastatic effects of HIF involve a broad transcriptional program that influences multiple steps in the metastatic phenotype. Dr. Kim continues to be active in the field of solid tumor hypoxia (4).

1. **Kim WY**, Safran M, Buckley MRM, Ebert BL, Glickman J, Bosenberg M, Regan M, Kaelin WG. Failure to prolyl hydroxylate hypoxia-inducible factor alpha phenocopies VHL inactivation in vivo. *EMBO J.* 2006 Oct 4;25(19):4650–62. PMCID: PMC1589988
2. **Kim WY***, Perera S, Zhou B, Carretero J, Yeh JJ, Heathcote SA, Jackson AL, Nikolinakos P, Ospina B, Naumov G, Brandstetter KA, Weigman VJ, Zaghlul S, Hayes DN, Padera RF, Heymach JV, Kung AL, Sharpless NE, Kaelin WG, Wong K-K. HIF2alpha cooperates with RAS to promote lung tumorigenesis in mice. *J. Clin. Invest*. 2009 Aug;119(8):2160–70. PMCID: PMC2719950 * Corresponding author.
3. Hanna SC, Krishnan B, Bailey ST, Moschos SJ, Kuan P-F, Shimamura T, Osborne LD, Siegel MB, Duncan LM, O'Brien ET, Superfine R, Miller CR, Simon MC, Wong K-K, **Kim WY**. HIF1α and HIF2α independently activate SRC to promote melanoma metastases. *J. Clin. Invest.* 2013 May 1;123(5):2078–93. PMCID: PMC3635738
4. Yeh JJ, **Kim WY**. Targeting Tumor Hypoxia With Hypoxia-Activated Prodrugs. *Journal of Clinical*

Oncology. 2015 Mar 23;33(13):1505–8.

The identification of distinct intrinsic RNA subtypes of high-grade bladder cancer and NextGen Sequencing.

Based on the clinical heterogeneity of high-grade bladder cancer (urothelial carcinoma) we hypothesized that we could subclassify high-grade bladder cancer into intrinsic molecular subtypes based on their RNA expression. In this way we could help distinguish subtypes of bladder cancer that a pathologist would not classify differently but that we could differentiate molecularly. Using global transcriptome profiling of bladder cancers we have defined intrinsic subtypes of bladder cancer, which we have termed basal, luminal, and claudin-low that have distinct epidemiological associations and importantly differences in overall survival, even with multivariate testing (5). Therefore, the Kim Lab has been a leader in the field of RNA subtyping of bladder cancer and were significantly involved in the RNA expression analysis of the TCGA Bladder Cancer Project. The Kim Lab has also recently identified a claudin-low subtype of bladder cancer that is heavily immune infiltrated (6). In addition, Dr. Kim is experienced in the NextGen sequencing of human and mouse cancer genomes as the Chair of the Clinical Committee for Genomic Research for the Lineberger's UNCseq^{TM} clinical sequencing initiative as well as the Director for Genomic Research for UNC's Mouse Phase 1 Unit (MP1U) respectively (7). Recent work also includes identifying genomics of racial disparities (8).

5. Damrauer JS, Hoadley KA, Chism DD, Fan C, Tiganelli CJ, Wobker SE, Yeh JJ, Milowsky MI, Iyer G, Parker JS, **Kim WY**. Intrinsic subtypes of high-grade bladder cancer reflect the hallmarks of breast cancer biology. *Proceedings of the National Academy of Sciences*. 2014 Feb 25;111(8):3110–5. PMCID: PMC3939870
6. Kardos J*, Chai S*, Mose LE, Selitsky, SR, Krishnan B, Saito R, Iglesia MD, Milowsky MI, Parker JS, **Kim WY#,** and Vincent BG#. Claudin-low bladder tumors are immune infiltrated and actively immune suppressed. *JCI Insight*. 2016 Mar 17;1(3):e85902. PMID: 27699256. PMCID: PMC5033914
7. Hayes DN, **Kim WY**. The next steps in next-gen sequencing of cancer genomes. *J. Clin. Invest*. 2015 Feb 2;125(2):462–8. PMID: 25642706. PMC4319423.
8. Krishnan BV, Rose TL, Kardos J, Milowsky MI, **Kim WY**. Intrinsic genomic differences between African-Americans and Caucasians with clear cell renal cell carcinoma. *JAMA Oncology*. 2016 Mar 24. doi: 10.1001/jamaoncol.2016.0005. [Epub ahead of print]. PMID: 27010573

JAK/STAT pathway in tumorigenesis.

The Kim Lab has also worked on the JAK/STAT pathway in tumorigenesis. Specifically, they were involved as significantly contributing to the understanding of how specific mutations of VHL called Chuvash Polycythemia mutants, *VHL^{R200W}*, result in enhanced signaling from the erythropoietin (EPO) receptor (EPOR) (9). Furthermore, the lab has demonstrated that erythropoietin promotes breast cancer progression in genetically engineered mouse models through promoting tumor initiating cell self-renewal and enhancing JAK/STAT signaling (10). Moreover, the Kim lab has worked extensively with JAK inhibitors in mouse models demonstrating its efficacy in Chuvash polycythemia (9) as well as their ability to synergize with chemotherapy in breast GEM models (10).

9. Russell RC, Sufan RI, Zhou B, Heir P, Bunda S, Sybingco S, Roche O, Heathcote SA, Chow VWK, Greer SN, Boba LM, Richmond TD, Hickey MM, Barber DL, Cheresh DA, Simon MC, Irwin MS, **Kim WY**, Ohh M, *Loss of JAK2 regulation via VHL-SOCS1 E3 ubiquitin heterocomplex underlies chuvash polycythemia. Nat Med*, 2011 Jun 19;17(7):845-53. PMID: 21685897
10. Zhou B*, Damrauer JS*, Hadzic T, Jeong Y, Clark K, Fan C, Murphy L, Lee CY, Troester MA, Miller CR, Jin J, Darr D, Perou CM, Levine R, Diehn M, and **Kim WY**. Erythropoietin promotes breast tumorigenesis through tumor initiating cell self-renewal. *equal contribution. *Journal of Clinical Investigation,* 2014, Feb 3;124(2):553-63. PMID: 24435044

Genetically engineered murine models of cancer.

During his post-doctoral fellowship in the Kaelin Lab at Dana-Farber Dr. Kim generated 2 novel mouse strains, which allow the Cre inducible expression of HIF1α and HIF2α (11). In addition, Dr. Kim has written review articles on the drug efficacy testing in GEM models (12) as well as worked collaboratively with the Magnuson Lab (UNC) to develop the first GEM model of clear cell ovarian carcinoma, based on Adeno-Cre injections into

the ovarian bursa (14). The Kim Lab has also recently published 2 novel GEM models of renal cell carcinoma (RCC): a MYC driven model of papillary RCC and one in which concurrent Vhl and Cdkn2a inactivation when combined with MYC overexpression gives rise to clear cell RCC (14). Therefore, Dr. Kim has significant experience with the development and characterization of GEM models of cancer as well as applying them for furthering our understanding of cancer biology.

11. **Kim WY**, Safran M, Buckley RM, Ebert, BL, Glickman J, Bosenberg M, Regan M, Kaelin WG, Jr. Failure to prolyl hydroxylate hifa phenocopies vhl inactivation in vivo. *EMBO Journal*. 2006 Oct 4;25(19):4650-62. PMID: 16977322. PMCID: PMC1589988.
12. **Kim WY** and Sharpless NE. Drug Efficacy Testing in Mice. *Curr Top Microbiol Immunol*. 2011 Aug 7. PMID: 21823029. PMCID: PMC3732649
13. Chandler RL*, Damrauer JS*, Raab J, Schisler JC, Wilkerson MD, Didion JP, Starmer J, Serber D, Yee D, Xiong J, Darr D, Pardo-Manuel de Villena F, **Kim WY**, Magnuson T. Coexistent ARID1A-PIK3CA mutations promote ovarian clear cell tumorigenesis through pro-tumorigenic inflammatory cytokine signaling. *Nature Communications*, 2015 Jan 27;6:6118. PMID: 25625625. PMCID - in process.
14. Bailey ST*, Smith AM*, Kardos J, Wobker SE, Wilson HL, Krishnan B, Saito R, Lee HJ, Zhang J, Eaton SC, Williams LA, Manocha U, Peters DJ, Pan X, Carroll TJ, Felsher DW, Walter V, Zhang Q, Parker JS, Yeh JJ, Moffitt RA, Leung JY[#], **Kim WY[#]**. MYC activation cooperates with Vhl and Ink4a/Arf loss to induce clear cell renal cell carcinoma. *Nature Communications*. 2017 Jun 8;8:15770. PMID: 28593993. * equal contribution

Full List of Publications.
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40561006/?sort=date&direction=descending