BIOGRAPHICAL SKETCH

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NAME: RATHMELL, WENDY KIMRYN

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

POSITION TITLE: Professor of Medicine, Chair

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)	Completion Date MM/YYYY	FIELD OF STUDY
University of Northern Iowa, Cedar Falls, IA	BA	05/1991	Chemistry
University of Northern Iowa, Cedar Falls, IA	BS	05/1991	Biology
Stanford University, Stanford, CA	PHD	06/1996	Biophysics
Stanford University, Stanford, CA	MD	06/1998	Medicine
University of Chicago, Chicago, IL	Resident	06/1999	Intern
University of Pennsylvania, Philadelphia, PA	Resident	06/2000	Internal Medicine
University of Pennsylvania, Philadelphia, PA	Fellow	06/2004	Medical Oncology

A. Personal Statement

I am a physician-scientist with a cancer biology research program focused on understanding the relationships between genetic events and the development of renal cancers (RCC). We work from the ground up to understand the key genetic and molecular events contributing to the progression of this disease, using animal models and human tissue studies to define these events. As a leader on The Cancer Genome Atlas for renal cell carcinomas, we made numerous new discoveries for these cancers, which my laboratory is new delving into to understand mechanistically. Our work has ranged from interrogating tumor angiogenesis and hypoxia signaling, generation of VHL models of disease, and mediators of metastasis and migration. Recent discoveries of chromatin modifiers as mutation targets in RCC has caused us to direct studies in this direction, revealing new insights into how chromatin organization is impacted in transformation, and identifying novel activities of the chromatin modifier SETD2. These studies examine the impact of alterations in the epigenetic landscape of renal cell carcinoma, altering transcriptional fidelity as well as endogenous retrovirus expression.

The next horizon in RCC will be in understanding the specific events that enable metastasis, the state that drives lethality. We are well positioned with human models, ranging from tissue banks and tissue microarrays, to patient derived organoids that retain the cellular admixture of the primary tumor environment.

B. Positions and Honors

Positions and Employment

2003 - 2004	Instructor, University of North Carolina at Chapel Hill, Chapel Hill, NC
2004 - 2015	Assist. Professor, Assoc Prof. Department of Medicine, Department of Genetics, UNC
2011 - 2015	Alexander Professor in Translational Studies and Associate Director for Transl. Research, MD-PhD Training Program (MSTP), UNC
2012 - 2015	Associate Professor, Department of Urology (founding member), UNC
2014 - 2015	Assoc. Director for Education and Training, Lineberger Comprehensive Cancer Center, UNC
2015 - 2019	Director, Division of Hematology and Oncology, Vanderbilt University, Nashville, TN
2015 - 2020	Cornelius Abernathy Craig Professor of Medicine, Biochemistry (Secondary), VUMC
2019 -	Dep. Dir. for Research Integration and Career Development, Vanderbilt-Ingram Cancer Center
2020 -	Chairman, Department of Medicine, Hugh J. Morgan endowed chair, VUMC
2020 -	Physician-in-Chief, Vanderbilt University Hospital

Other Experience and Professional Memberships

2003 -	American Association for Cancer Research: Member; abstract review, grant review committee
2003 -	American Society of Clinical Oncology: Member, Fellows & Junior Faculty Track Task Force, Leadership Development Program, Ethics Committee, Education Committee (Tumor Biology, track leader), Nominating Committee (2020 Chair, elected position)
2004 - 2024	Diplomat in Medical Oncology, American Board of Internal Medicine
2010 - 2013	Department of Defense: CDMRP Integration Panel
2010 - 2016	American Cancer Society: Tumor Biology and Genetics Study Section
2012 - 2017	Editorial Board-Cancer Research, Editorial Board, Associate Editor, J Clin Invest
2013 - 2016	NCI-J, BMCT-C, F09B, MONC Study Sections (Ad Hoc), NCI
2014 - 2015	Scholar Retreat Chair, Forbeck Foundation for Cancer Research
2014 - 2017	American Society of Clinical Investigation: Council Member, Secretary Treasurer
2016 -	Kidney Cancer Research Alliance: Scientific Advisory Board
2017 - 2021	Department of Defense: Kidney Cancer Research Program, Integration Panel, Chair
2017 - 2021	American Society of Clinical Investigation: Vice President, President-Elect, President (2019)
2017 -	National Cancer Institute, Board of Scientific Advisors
2018 - 2021	Harrington Prize Selection Committee, Harrington Institute
2019 - 2024	Paul Marks Prize for Cancer Research Selection Committee
2019 -	Burroughs Wellcome CAMS Steering Committee
2020 -	Damon Runyon Physician Scientist Training Award Scientific Committee

Honors

1987 - 1991	Presidential Scholar, University of Northern Iowa
1991	Purple and Old Gold Award (Top Graduate-Chemistry), University of Northern Iowa
1994	Howard Hughes Predoctoral Fellowship, Howard Hughes Medical Institute
1996	PEO Scholar Award, PEO International
2003	V Scholar Award, V Foundation for Cancer Research
2004	Forbeck Scholar, Forbeck Foundation
2006	Doris Duke Clinical Scientist, Doris Duke Foundation
2010	AACR Landon INNOVATOR Award, American Association for Cancer Research
2011	ASCI, American Society of Clinical Investigation Inductee
2012	Ruth and Phillip Hettleman Award, University of North Carolina at Chapel Hill
2014	Alpha Omega Alpha (AOA), University of North Carolina at Chapel Hill
2015	Leland Wilson Alumni Speaker, University of Northern Iowa
2018	AAP, American Association of Physicians Inductee
2019	Eugene P. Schonfeld Award, Kidney Cancer Association
2019	Greenbrier Louisa Nelson Nashville Women of Influence Award
2020	American Association for the Advancement of Science, Elected Fellow

C. Contribution to Science

1. We developed the first validated biomarker gene expression signatures for clear cell type renal cell carcinoma, ccA and ccB, which define biologic subgroupings and function as effective prognostic tools for estimating risk for disease recurrence. This biomarker tool has been independently verified by several independent groups as a risk prediction tool. We are now expanding our biomarker work to include immune response modifiers, endogenous retroviral elements, and have examined proteomic signatures of kidney cancers as biomarkers.

    a. Brooks SA, Khandani AH, Fielding JR, Lin W, Sills T, Lee Y, Arreola A, Milowsky MI, Wallen EM, Woods ME, Smith AB, Nielsen ME, Parker JS, Lalush DS, **Rathmell WK**. Alternate Metabolic Programs Define Regional Variation of Relevant Biological Features in Renal Cell Carcinoma Progression. *Clin Cancer Res.* 2016 Jun 15;22(12):2950-9. PMID: 26787754; PMCID: PMC4911278.

    b. Smith CC, Beckermann KE, Bortone DS, de Cubas AA, Bixby LM, Lee SJ, Panda A, Ganesan S, Bhanot G, Wallen EM, Milowsky MI, Kim WY, **Rathmell WK**, Swanstrom R, Parker JS, Serody JS,

Selitsky SR, Vincent BG. Endogenous retroviral signatures predict immunotherapy response in clear cell renal cell carcinoma. *J Clin Invest*. 2018 Aug 23. PMID: 30137025, PMCID: PMC6205406.

c. Panda A, de Cubas AA, Stein M, Riedlinger G, Kra J, Mayer T, Smith CC, Vincent BG, Serody JS, Beckermann KE, Ganesan S, Bhanot G, **Rathmell WK.** Endogenous retrovirus expression is associated with response to immune checkpoint blockade in clear cell renal cell carcinoma. *JCI Insight.* 2018 Aug 23;3(16). PMID: 30135306 PMCID: PMC6141170.

2. Our lab has a major effort examining the new class of chromatin modifier mutations as mediators of invasive phenotype and metastasis. In particular, we have used human tissues, yeast, and cell line model systems to discover novel tumor promoting activities contributing to the chromatin modifier mutant phenotype. Further, we recently discovered a second target of SETD2, microtubules, and are investigating this important area of potential genomic instability and regulation of transposable elements. In addition, we have worked in metabolism, and intersected transcription features with metabolic alteration.

   a. Chiang YC, Park IY, Terzo EA, Tripathi DN, Mason FM, Fahey CC, Karki M, Shuster CM, Sohn BH, Chowdhury P, Powell RT, Ohi R, Tsai YS, de Cubas AA, Khan A, Davis IJ, Strahl BD, Parker JS, Dere R, Walker CL, and **Rathmell WK.** SETD2 Haploinsufficiency for Microtubule Methylation is an Early Driver of Genomic Instability in Renal Cell Carcinoma. *Cancer Research*. 2018 Jun 15;78(12):3135-3146. PMID: 29724720. PMCID: PMC6004258

   b. Park IY, Powell RT, Tripathi DN, Dere R, Ho TH, Blasius TL, Chiang YC, Davis IJ, Fahey CC, Hacker KE, Verhey KJ, Bedford MT, Jonasch E, **Rathmell WK***, Walker CL*. Dual Chromatin and Cytoskeletal Remodeling by SETD2. *Cell.* 2016 Aug 11;166(4):950-62. PMID: 27518565; PMCID: PMC5101839.

   c. Hacker KE, Fahey CC, Shinsky SA, Chiang YJ, DiFiore JV, Jha DK, Vo AH, Shavit JA, Davis IJ, Strahl BD, **Rathmell WK**. Structure/Function Analysis of Recurrent Mutations in SETD2 Protein Reveals a Critical and Conserved Role for a SET Domain Residue in Maintaining Protein Stability and Histone H3 Lys-36 Trimethylation. *J Biol Chem*. 2016 Sep 30;291(40):21283-21295. PMID: 27528607; PMCID: PMC5076534.

   b. Simon JM, Hacker KE, Singh D, Brannon AR, Parker JS, Weiser M, Ho TH, Kuan PF, Jonasch E, Furey TS, Prins JF, Lieb JD, **Rathmell WK***, Davis IJ*. Variation in chromatin accessibility in human kidney cancer links H3K36 methyltransferase loss with widespread RNA processing defects. *Genome Res.* 2014 Feb;24(2):241-50. PMID: 24158655; PMCID: PMC3912414.

3. Our lab has recently turned to efforts to dissect the complex tumor microenvironment in renal cell carcinoma using freshly resected tissue. This work has implications for tumor classification, prognosis, detection, and therapy. We were the first to demonstrate the unique attributes of T cell dysfunction in renal cell carcinoma, and to show mechanisms to restore activation. The metabolic cues that drive activities of the TME are incredible, and we are dissecting the metabolic flux and demand from cell sets in this space, notably demonstrating the cell programmed partitioning of nutrients in vivo.

   a. Reinfeld BI, Madden MZ, Wolf MW, Chytil A, Bader JE, Patterson AR, Sugiura A, Cohen AS, Ali A, Do BT, Muir A, Lewis CA, Hongo RA, Young KL, Brown RE, Todd VM, Huffstater T, Abraham A, O'Neil RT, Wilson MH, Xin F, Tantawy MN, Merryman WD, Johnson RW, Williams CS, Mason EF, Mason FM, Beckermann KE, Vander Heiden MG, Manning HC, Rathmell JC*, **Rathmell WK*.** Cell Programmed Nutrient Partitioning in the Tumor Microenvironment. *Nature*. 2021. In press.

   b. Beckermann KE, Hongo R, Ye X, Young K, Carbonell K, Healey DCC, Siska PJ, Barone S, Roe CE, Smith CC, Vincent BG, Mason FM, Irish JM, **Rathmell WK***, Rathmell JC*. CD28 costimulation drives tumor-infiltrating T cell glycolysis to promote inflammation. JCI Insight. 2020 Aug 20;5(16):e138729. doi: 10.1172/jci.insight.138729. PMID: 32814710; PMCID: PMC7455120.

   c. Siska PJ, Beckermann KE, Mason FM, Andrejeva G, Greenplate AR, Sendor AB, Chiang YJ, Corona AL, Gemta LF, Vincent BG, Wang RC, Kim B, Hong J, Chen CL, Bullock TN, Irish JM, **Rathmell WK***, Rathmell JC*. Mitochondrial dysregulation and glycolytic insufficiency functionally impair CD8 T cells infiltrating human renal cell carcinoma. *JCI Insight*. 2017 Jun 15;2(12):e93411. doi: 10.1172/jci.insight.93411. PMID: 28614802; PMCID: PMC5470888.

   d. Vilgelm AE, Bergdorf K, Wolf M, Bharti V, Shattuck-Brandt R, Blevins A, Jones C, Phifer C, Lee M, Lowe C, Hongo R, Boyd K, Netterville J, Rohde S, Idrees K, Bauer JA, Westover D, Reinfeld B,

Baregamian N, Richmond A, **Rathmell WK**, Lee E, McDonald OG, Weiss VL. Fine-Needle Aspiration-Based Patient-Derived Cancer Organoids. *iScience*. 2020 Aug 21;23(8):101408. doi: 10.1016/j.isci.2020.101408. Epub 2020 Jul 24. PMID: 32771978; PMCID: PMC7415927.

4. The comprehensive genomic assessment of the somatic cancer genome provides a new way of understanding tumor biology and a resource for comparative, genetic, and molecular studies across the tumor types. I participated in the disease focused working groups, and co-led the first rare tumor project in the TCGA on chromophobe renal cell carcinoma, and the Pan-Kidney working group. This work has been critical to setting the stage for many of our investigations, and therefore reflects important output from our lab that combines expertise in cancer biology, clinical medicine, and computational methods.

   a. Linehan WM, Spellman PT, Ricketts CJ, Creighton CJ, Fei SS, Davis C, Wheeler DA, Murray BA, Schmidt L, Vocke CD, Peto M, Al Mamun AA, Shinbrot E, Sethi A, Brooks S, **Rathmell WK***, et. al. Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma. *N Engl J Med.* 2016 Jan 14;374(2):135-45. PMID: 26536169; PMCID: PMC4775252. *Lead writing team.

   b. Davis CF, Ricketts CJ, Wang M, Yang L, Cherniack AD, Shen H, Buhay C, Kang H, Kim SC, Fahey CC, Hacker KE, Bhanot G, Gordenin DA, Chu A, Gunaratne PH, Biehl M, Seth S, Kaipparettu BA, Bristow CA, Donehower LA, Wallen EM, Smith AB, Tickoo SK, Tamboli P, Reuter V, Schmidt LS, Hsieh JJ, Choueiri TK, Hakimi AA, Chin L, Meyerson M, Kucherlapati R, Park WY, Robertson AG, Laird PW, Henske EP, Kwiatkowski DJ, Park PJ, Morgan M, Shuch B, Muzny D, Wheeler DA, Linehan WM, Gibbs RA, **Rathmell WK***, Creighton CJ*. The somatic genomic landscape of chromophobe renal cell carcinoma. *Cancer Cell.* 2014 Sep 8;26(3):319-30. PMID: 25155756; PMCID: PMC4160352. *Co-corresponding author, *Analysis Working Group Co-leader.

   c. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of clear cell renal cell carcinoma. *Nature*. 2013 Jul 4;499(7456):43-9. PMID: 23792563; PMCID: PMC3771322. *Lead transcription analysis, *Lead writing team.

   d. Ricketts, CJ, De Cubas AA, Fan H, Smith CC, Lang M, Reznik E, Bowlby R, Gibb EA, Akbani R, Beroukhim R, Bottaro DP, Choueiri TK, Gibbs RA, Godwin AK, Haake SM, Hakimi AA, Henske EP, Hsieh JJ, Ho TH, Kanchi R, Krishnan B, Kwaitkowski DJ, Lui W, Merino MJ, Mills GB, Myers J, Nickerson ML, Reuter VE, Schmidt LS, Shelley CS, Shen H, Shuch B, Signoretti S, Srinivasan R, Tamboli P, Thomas G, Vincent BG, Vocke CD, Wheeler DA, Yang L, Kim WY, Robertson AG, The Cancer Genome Atlas Research Network, Spellman PT*, **Rathmell WK*,** Linehan WM*. The Cancer Genome Atlas Comprehensive Molecular Characterization of Renal Cell Carcinoma. *Cell Reports*, 2018 Apr 3;23(1):313-326.e5. PMID: 29617669 PMCID: PMC6075733. *Co-corresponding.

5. We have been working from numerous angles to develop novel therapeutics for the treatment of renal cell carcinoma. This translational work includes basic laboratory preclinical studies to discover or advance therapeutic strategies, or novel clinical trials designed to reveal windows for treatment intervention or unique vulnerabilities. We have been active in testing therapies as well as functional imaging studies in this disease to utilize molecular mechanisms to realize opportunities in the clinic.

   a. Wood CG, Ferguson JE 3rd, Parker JS, Moore DT, Whisenant JG, Maygarden SJ, Wallen EM, Kim WY, Milowsky MI, Beckermann KE, Davis NB, Haake SM, Karam JA, Bortone DS, Vincent BG, Powles T, **Rathmell WK**. Neoadjuvant pazopanib and molecular analysis of tissue response in renal cell carcinoma. *JCI Insight*. 2020 Nov 19;5(22):e132852. doi: 10.1172/jci.insight.132852. PMID: 33208553; PMCID: PMC7710285.

   b. McDermott DF, Huseni MA, Atkins MB, Motzer RJ, Rini BI, Escudier B, Fong L, Joseph RW, Pal SK, Reeves JA, Sznol M, Hainsworth J, **Rathmell WK**, Stadler WM, Hutson T, Gore ME, Ravaud A, Bracarda S, Suárez C, Danielli R, Gruenwald V, Choueiri TK, Nickles D, Jhunjhunwala S, Piault-Louis E, Thobhani A, Qiu J, Chen DS, Hegde PS, Schiff C, Fine GD, Powles T. Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. *Nat Med*. 2018 Jun;24(6):749-757. Epub 2018 Jun 4. Erratum in: Nat Med. 2018 Dec;24(12):1941. PMID: 29867230; PMCID: PMC6721896.

   c. Arreola A, Payne LB, Julian MH, de Cubas AA, Daniels AB, Taylor S, Zhao H, Darden J, Bautch VL, **Rathmell WK**, Chappell JC. Von Hippel-Lindau mutations disrupt vascular patterning and maturation via Notch. *JCI Insight*. 2018 Feb 22;3(4):e92193. PMID: 29467323; PMCID: PMC5916240.

d. de Cubas AA, Dunker W, Zaninovich A, Hongo RA, Bhatia A, Panda A, Beckermann KE, Bhanot G, Ganesan S, Karijolich J, **Rathmell WK**. DNA hypomethylation promotes transposable element expression and activation of immune signaling in renal cell cancer. *JCI Insight.* 2020 Jun 4;5(11):e137569. PMID: 32493845 PMCID: PMC7308050

Published Works (of >200) in My Bibliography: https://pubmed.ncbi.nlm.nih.gov/?term=rathmell+wk&sort=date

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R01 CA198482, NCI RATHMELL, WENDY (MPI, with DAVIS, I; STRAHL, B) 09/30/15-08/31/20
Chromatin maintenance in cancer progression (No cost extension)
This study examines links between chromatin marks, transcription, and sites of DNA damage.
Role: Corresponding PI

R01 CA203012, NCI RATHMELL, WENDY (MPI, with WALKER, C) 07/01/16-06/30/21
Methyltransferase Contributions to Genomic Stability and Cancer
This project examines novel activities of SETD2 in promoting genomic instability and cancer.
Role: Corresponding PI

R01 CA217987-01 RATHMELL, JEFF (PI) 04/01/18-03/31/23
Metabolic Barriers to T Cell Activation in Clear Cell Renal Cell Carcinoma
Role Co-I

K12 CA090625-16, NIH RATHMELL, WENDY (PI) 07/01/16-06/30/21
Vanderbilt Clinical Oncology Research Career Development Award
This award supports the career development of cancer-focused translational researchers.
Role: PI

T32 CA217834-01 NIH RATHMELL, WENDY (PI) 08/01/18-07/31/23
Vanderbilt Integrated Molecular Oncology Research Training Program (VIMO-RTP)
This award supports the career development of cancer-focused translational researchers in clinical training.
Role: PI

ORIEN New Oncologic Visionary Award (NOVA) GANESAN, SHRIDAR (PI) 08/01/19-07/31/22
Endogenous Retroviruses in Cancer Immunotherapy
Role: Co-I

Completed Research Support

K24 CA172355-01A1 RATHMELL, WENDY (PI) 07/01/13-06/30/18
Enhancing Translational Science via Prospective Investigation
Role: PI

AACR-Kure It Research Grant for Immunotherapy in Kidney Cancer 07/01/18-06/30/20
Immunosuppression in the RCC tumor microenvironment
Role: PI