BIOGRAPHICAL
SKETCH

NAME: Charles Willard Mortimer Roberts, MD, PhD

eRA COMMONS USER NAME: charles_roberts

POSITION TITLE: Director, Comprehensive Cancer Center, St. Jude Children's Research Hospital

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Wisconsin – Madison	BS	/1984	Zoology
Washington University, St. Louis, MO	MD, PhD	/1995	Medicine/Immunology
Children's Hospital Boston, MS	Internship Training	/1995-1996	Pediatrics
Children's Hospital Boston	Medical Residency	/1996-1997	Pediatrics
Children's Hospital Boston / Dana-Farber Cancer Institute, Boston, MA	Subspecialty Fellowship	/1997-2001	Pediatric Hematology-Oncology

A. Personal Statement

The central focus of my laboratory is upon understanding the role of SWI/SNF (BAF) complex mutations in cancer. This began at the start of my post-doctoral studies when SMARCB1/SNF5 was found to be mutated in aggressive pediatric rhabdoid cancers. Since that time, I and my laboratory have studied both the normal function of the complex and its role as a tumor suppressor with accomplishments highlighted below. We make use of diverse models including genetically engineered mouse models, primary cells derived from them, and cancer cell lines. My laboratory has contributed key advances in understanding how mutations in SWI/SNF complexes give rise to malignancy and in identification of vulnerabilities that arise as a result of SWI/SNF mutations. These discoveries have been translated into investigational and FDA-approved cancer therapies for both children and adults

1. Kim KH, Woojin K, Howard TP, Vazquez F, Tsherniak A, Wu JN, Wang W, Haswell JR, Walensky LD, Hahn WC, Orkin SH, **Roberts CWM**. SWI/SNF-mutant cancers depend upon catalytic and non-catalytic activity of EZH2. Nature Medicine 2015, Dec;21(12):1491-6 PMID: 26552009. PMCID: PMC4886303
2. Mathur R, Alver BH, San Roman AK, Wilson BG, Wang X, Agoston AT, Park PJ, Shivdasani RA and **Roberts CWM**. ARID1A loss impairs enhancer-mediated gene regulation and drives colon cancer in mice. Nature Genetics 2017; 49: 296-302. PMID: 27941798. PMCID: PMC5285448.
3. Wang X, Lee, RS, Alver BH, Haswell JR, Wang S, Mieczkowski J, Drier Y, Gillespie SM, Archer TC, Wu JN, Tzvetkov EP, Troisi EC, Pomeroy SL, Biegel JA, Tolstorukov MY, Bernstein BE, Park PJ, and **Roberts CWM**. SMARCB1-mediated SWI/SNF complex function is essential for enhancer regulation. Nature Genetics 2017; 49: 289-295. PMID: 27941797. PMCID: PMC5285474
4. Drosos Y, Myers JA, Xu B, Mathias KM, Beane EC, Radko-Juettner S, Mobley RJ, Larsen ME, Piccioni F, Ma X, Low J, Hansen BS, Peters ST, Bhanu NV, Dhanda SK, Chen T, Upadhyaya SA, Pruett-Miller SM, Root DE, Garcia BA, Partridge JF, **Roberts CWM**. NSD1 mediates antagonism between SWI/SNF and Polycomb complexes and is required for transcriptional activation upon EZH2 inhibition. Molecular Cell 2022 Jul 7; 82(13):2472-2489.e8. PMID: 35537449

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2001-2003 Instructor in Pediatric Hematology-Oncology, Children's Hospital Boston / Dana-Farber Cancer Institute, Boston, MA

2003-2010 Assistant Professor of Pediatric Hematology-Oncology, Dana-Farber Cancer Institute I Children's Hospital Boston/Harvard Medical School, Boston, MA

2011-2015 Associate Professor of Pediatric Hematology-Oncology, Dana-Farber Cancer Institute/ Boston Children's Hospital/ Harvard Medical School, Boston, MA

2015-Present Director, Comprehensive Cancer Center, Executive Vice President, and Member, St. Jude Children's Research Hospital, Memphis, TN

Honors

1987 Knapp-Brittingham Research Award, University of Wisconsin

1988-1995 Medical Scientist Training Program Awardee, Washington University

1993 Spencer T. and Ann W. Olin Medical Scientist Fellowship

1995 George F. Gill Prize in Pediatrics, Washington University

1995 Alpha Omega Alpha Medical Honor Society, Washington University

2003 "Outstanding Presentation" award at Children's Hospital research day

2003 American Association for Cancer Research Scholar-in-Training Award

2004 Stephen E. Sallan Leadership Award. This award recognizes Pediatric Oncology staff "Who are our leaders... for their ability to guide, inspire and motivate others".

2007 Elected to membership in the Society for Pediatric Research.

2010 Elected to membership in the American Society of Clinical Investigation.

2012 Tal Doran Keynote address, Rhabdoid tumors, 151st annual International Symposium on Pediatric Neuro-Oncology, Toronto, Ontario, Canada

2013 Selected by the American Association of Cancer Research to Co-Chair a Special Conference on "Chromatin and Epigenetics in Cancer", Atlanta, GA

2013 Presented Keynote address, at International meeting on Rhabdoid Tumors: Integrating Biological Insights with Clinical Success, Paris, France.

2014 Keynote address at The Marsha Rivkin Center for Ovarian Cancer Research & The AACR 1Oth Biennial Ovarian Cancer Research Symposium, Seattle, WA.

2014 Elected to membership in the American Pediatric Society.

2015 Selected by the American Association of Cancer Research to Co-Chair a Special Conference on "Chromatin and Epigenetics in Cancer", Atlanta, GA

2015 Invited participant for Nature Medicine and Volkswagen Foundation "Cancer Genomics and Tumor Heterogeneity" Herrenhausen Symposium. Hannover, Germany

2017 Selected by the American Association of Cancer Research to Co-Chair a Special Conference on "Pediatric Cancer", Atlanta, GA

2017 Keynote address at American Association for Cancer Research special conference on Advances in Sarcomas: From Basic Science to Clinical Translation, Philadelphia, PA

2017 Selected by the Washington University Medical Center Alumni Association as the recipient of the 2017 Alumni Achievement Award.

2018 Keynote address at International Rhabdoid Tumor Meeting, Lake Louise, Canada

2018 Elected to membership in the Association of American Physicians

2019 Keynote address at Genetic Predisposition to Primary CNS Cancers "Think Tank", Columbus, Ohio

2020 Plenary talk at the New Approaches to Neuroblastoma Therapy (NANT) annual meeting, Los Angeles, CA.

C. Contribution to Science

1) As a graduate student in the laboratory of Dr. Stanley Korsmeyer at Washington University in St. Louis, I began a search to understand mechanisms by which gene mutations drive cancer formation and focused on the t(10;14) chromosomal translocation in T-ALL. I identified the transcript specifically deregulated by this translocation (Zutter et al., PNAS), collaborated with a post-doc to identify it as the transcription factor Hox11 (Hatano et al., Science). I then utilized emerging mouse knockout technology to understand the function of this gene in vivo and discovered that Hox11 controls the genesis of the spleen (Roberts et al, Nature and AJP). This work contributed to the newly recognized theme that the chromosomal translocations in leukemia drive cancer by causing uncontrolled expression of master regulatory transcription factors.

a. Hatano M, **Roberts CWM**, Minden M, Crist WM, Korsmeyer SJ. Deregulation of a homeobox gene, HOX11, by the t(10;14) in T cell leukemia. Science 1991; 253: 79-82.

b. **Roberts CWM**, Shutter JR, Korsmeyer SJ. Hox11 controls the genesis of the spleen. Nature 1994; 368: 747-749

c. **Roberts CWM**, Sander AM, Lumsden AGS, Korsmeyer SJ. Developmental expression of Hox11 and specification of splenic cell fate. American Journal of Pathology. 1995; 146:1089-1101.

2) During my post-doctoral studies in the laboratory of Dr. Stuart Orkin, I continued my pursuit to understand the mechanisms that drive cancer formation by investigating a gene, SNF5 (INI1/SMARCB1), newly identified as inactivated in a lethal pediatric cancer called malignant rhabdoid tumor. SNF5, a core member of the SWI/SNF chromatin remodeling complex, represented the first known link between ATP-dependent chromatin remodeling complexes and cancer, and thus offered the potential for novel insights into mechanisms of oncogenesis. Using genetically engineered mouse modeling, we demonstrated that SNF5 is a bona fide tumor suppressor (Roberts, PNAS) and that its conditional inactivation results in extremely rapid cancer onset in all mice, (Roberts, Cancer Cell; Roberts, Nature Reviews Cancer). Launching my own laboratory, we began to provide mechanistic insight by demonstrating a role for Snf5 in control of cell cycle progression (Isakoff et al, PNAS).

a. **Roberts CWM**, Galusha SA, McMenamin ME, Fletcher COM and Orkin SH. Haploinsufficiency of Snf5 (integrase interactor 1) predisposes to malignant rhabdoid tumors in mice. Proceedings of the National Academy of Sciences, USA 2000; 97: 13796-13800.
b. **Roberts CWM**, Leroux MM, Fleming MD, Orkin SH. Highly penetrant, rapid tumorigenesis through conditional inversion of the tumor suppressor gene Snf5. Cancer Cell 2002; 2: 415-425.
c. Isakoff MS, Sansam CG, Tamayo P, Subramanian A, Evans JA, Fillmore CM, Wang X, Biegel JA, Pomeroy SL, Mesirov JP and **Roberts CWM**. Inactivation of the Snf5 tumor suppressor stimulates cell cycle progression and cooperates with p53 loss in oncogenic transformation. Proceedings of the National Academy of Sciences, USA 2005; 102: 17745-17750.

3) Having established SNF5/SMARCB1 and the SWI/SNF complex as potent tumor suppressors, a key question was whether mutation of the complex drives cancer by deregulating transcription or by resulting in genomic instability and DNA damage. We found that SNF5 loss drove cancer without detectable activation of DNA damage pathways and gave rise to diploid cancers that were genomically stable (McKenna et al., MCB). We showed that the genomes of pediatric malignant rhabdoid tumors were remarkably simple (Lee, JCI and Lawrence, Nature). From a transcriptional standpoint, we demonstrated that SNF5 and the SWI/SNF complex function to control nucleosome occupancy to regulate transcription (Tolstorukov PNAS). Collectively, our work demonstrated that high mutation rates are dispensable for the genesis of cancers driven by mutation of a chromatin remodeling complex and that mutation of SNF5 likely drives cancer by impairing normal transcriptional control. Our recent work in collaborating on the establishment of the Pediatric Cancer Dependency Map (Dharia et al.) has revealed that vulnerabilities in rhabdoid tumors most frequently map to chromatin regulation.

a. Lee RS, Stewart C, Carter SL, Ambrogio L, Cibulskis K, Sougne C, Lawrence MS, Auclair D, Mora J, Golub TR, Biegel JA, Getz G, and **Roberts CWM**. A remarkably simple genome underlies highly malignant pediatric rhabdoid cancers. Journal of Clinical Investigation 2012; 122: 2983-2988. PMID: 22797305 PMCID: PMC3408754
b. Lawrence MS, Stojanov P, Polak P, Kryukov GV, Cibulskis K, Sivachenko A, Carter SL, Stewart C, Mermel CH, Roberts SA, Kiezun A, Hammerman PS, McKenna A, Drier Y, Zou L, Ramos AH, Pugh TJ, Stransky N, Helman E, Kim J, Sougnez C, Ambrogio L, Nickerson E, Shetler E, Cortes ML, Auclair D, Saksena G, Saksena G, Voet D, Noble M, DiCara D, Lin P, Lichtenstein L, Jing R, Fennell T, Imielinski M, Hernandez B, Hodis E, Baca S, Dulak AM, Lohr J, Landau DA, Wu CJ, Melendez-Zajgla J, Hidalgo-Miranda A, Koren A, McCarroll SA, Mora J, Crompton B, Onofrio R, Parkin M, Winckler W, Ardlie K, Gabriel SB, **Roberts CWM**, Biegel JA, Stegmaier K, Bass A, Garraway LA, Meyerson M, Golub TR, Gordenin DA, Sunyaev S, Lander ES, and Getz G. Mutational heterogeneity in cancer and the search for new cancer genes. Nature 2013; 499: 214-8. PMID: 23770567 PMCID: PMC3919509
c. Wang X, Lee, RS, Alver BH, Haswell JR, Wang S, Mieczkowski J, Drier Y, Gillespie SM, Archer TC, Wu JN, Tzvetkov EP, Troisi EC, Pomeroy SL, Biegel JA, Tolstorukov MY, Bernstein BE, Park PJ, and **Roberts CWM**. SMARCB1-mediated SWI/SNF complex function is essential for enhancer regulation. Nature Genetics 2017; 49: 289-295. PMID: 27941797. PMCID: PMC5285474
d. Dharia NV, Kugener G, Guenther LM, Malone CF, Durbin AD, Hong AL, Howard TP, Bandopadhayay P, Wechsler CS, Fung I, Warren AC, Dempster JM, Krill-burger JM, Paolella BR, Moh P, Jha N, Tang A, Montgomery P, Boehm JS, Hahn WC, **Roberts CWM**, McFarland JM, Tsherniak A, Golub TR, Vazquez F, Stegmaier K. A First-Generation Pediatric Cancer Dependency Map. Nature Genetics, 2021, PMID: 33753930, PMCID: PMC8049517.

4) We next sought to understand the mechanisms by which mutation of SMARCB1/SNF5 drives cancer onset. We identified the existence of epigenetic antagonism between SNF5 and the Polycomb enzyme EZH2 and showed that inactivation of Ezh2 blocks tumor formation driven by Snf5 loss in vivo (Wilson, Cancer Cell) and that this dependency broadly extends to SWI/SNF mutant cancers (Kim, Nature Medicine). We also identified transcriptional programs activated by SNF5 loss that drive the cancer phenotype (Jagani, Nature Medicine). Using our mouse models, we investigated lymphoma caused by Snf5 loss and found that Snf5 loss causes

transformation of an extremely specific cell type: a subset of CD8+ memory T cells (Wang, JCI; Wilson, Nature Reviews Cancer). This work identified a chromatin based mechanism that drives cancer, identified pathways underlying transformation, and revealed that the cancer promoting activity is restricted to highly specific developmental states suggesting that perturbation of normal developmental pathways is central to cancer caused by SNF5 loss. Importantly, the work in Wilson et al. served as the stimulus for clinical trials that in January of 2020 resulted in FDA approval of the EZH2 inhibitor Tazemetostat for SMARCB1-mutant sarcomas.

a. Wilson BG, Wang X, Shen X, McKenna ES, Lemieux ME, Cho YJ, Koellhoffer EC, Pomeroy SL, Orkin SH, **Roberts CWM**. Epigenetic antagonism between Polycomb and SWI/SNF complexes during oncogenic transformation. Cancer Cell 2010, Oct 19;18(4):316-28. PMID: 20951942 PMCID: PMC2957473
b. Kim KH, Woojin K, Howard TP, Vazquez F, Tsherniak A, Wu JN, Wang W, Haswell JR, Walensky LD, Hahn WC, Orkin SH, **Roberts CWM**. SWI/SNF-mutant cancers depend upon catalytic and non-catalytic activity of EZH2. Nature Medicine 2015, Dec;21(12):1491-6
c. Howard TP, Arnoff TE, Song MR, Giacomelli AO, Wang X, Hong AL, Dharia NV, Wang S, Vazquez F, Pham MT, Morgan AM, Wachter F, Bird GH, Kugener G, Oberlick EM, Rees MG, Tiv HL, Hwang JH, Walsh KH, Cook A, Krill-Burger JM, Tsherniak A, Gokhale PC, Park PJ, Stegmaier K, Walensky LD, Hahn WC, **Roberts CWM**. MDM2 and MDM4 Are Therapeutic Vulnerabilities in Malignant Rhabdoid Tumors. Cancer Research, 2019; 79:2404-2414
d. Drosos Y, Myers JA, Xu B, Mathias KM, Beane EC, Radko-Juettner S, Mobley RJ, Larsen ME, Piccioni F, Ma X, Low J, Hansen BS, Peters ST, Bhanu NV, Dhanda SK, Chen T, Upadhyaya SA, Pruett-Miller SM, Root DE, Garcia BA, Partridge JF and **Roberts CWM**. NSD1 mediates antagonism between SWI/SNF and Polycomb complexes and is required for transcriptional activation upon EZH2 inhibition. Molecular Cell 2022 Jul 7; 82(13):2472-2489.e8. PMID: 35537449

5) Given the high prevalence of mutations in SWI/SNF genes across cancer, an issue of major importance has been to identify dependencies conferred by SWI/SNF mutations as these would constitute potential therapeutic vulnerabilities. We discovered that cancer formation in the absence of SNF5 does not result from SWI/SNF inactivation but rather is dependent upon the activity of the residual SWI/SNF complex (Wang, Cancer Research). Subsequently, we discovered that the #1 vulnerability in ARID1A mutant cancer cell lines was ARID1B, another member of the SWI/SNF complex, and identified a mechanistic basis (Helming, Nature Medicine). We also discovered that the #1 vulnerability in SMARCA4 mutant cancers was SMARCA2 (Wilson, MCB). We also demonstrated that BRD9 defines a novel SWI/SNF sub-complex that lacks SMARCB1/SNF5 and that this complex constitutes a specific vulnerability in SMARCB1-mutant rhabdoid tumros. Collectively, these findings defined SWI/SNF complex families and identified the aberrant residual SWI/SNF complex as a therapeutic vulnerability in SWI/SNF mutant cancers. Leveraging a combination of high-dimensional drug screens across hundreds of cancer cell lines combined with genome-scale CRISPR dependency screens, we identified a strong vulnerability of rhabdoid tumors to the protein-translation inhibitor homoharringtonine (Howard et al.).

a. Helming KC, Wang X, Wilson BG, Vazquez F, Haswell JR, Manchester HE, Kim Y, Kryukov, Ghandi M, Aguirre AJ, Jagani Z, Wang Z, Garraway LA, Hahn WC, and **Roberts CWM**. ARID1B is a specific vulnerability in AR/01A-mutant cancers. Nature Medicine 2014; 20(3): 251-4. PMID: 24562383 PMCID: PMC3954704
b. Mathur R, Alver BH, San Roman AK, Wilson BG, Wang X, Agoston AT, Park PJ, Shivdasani RA and **Roberts CWM**. ARID1A loss impairs enhancer-mediated gene regulation and drives colon cancer in mice. Nature Genetics 2017; 49: 296-302. PMID: 27941798. PMCID: PMC5285448.
c. Wang W, Wang S, Troisi E, Howard T, Haswell J, Wolf B, Hawk W, Ramos P, Oberlick E, Tzvetkov E, Vazquez F, Hahn W, Park P, **Roberts CWM**. BRD9 defines a SWI/SNF sub-complex and constitutes a specific vulnerability in malignant rhabdoid tumors. Nature Communications 2019;10:1881. PMID:31015438, PMCID: PMC6479050
d. Howard TP, Oberlick EM, Rees MG, Arnoff TE, Pham MT, Brenan L, DoCarmo M, Hong AL, Kugener G, Chou HC, Drosos Y, Mathias K, Ramos P, Seashore-Ludlow B, Giacomelli AO, Wang X, Freeman III BB, Blakenship K, Hoffman L, Tiv HL, Gokhale PC, Johannessen CM, Stewart EA, Schreiber SL, Hahn WC, **Roberts CWM**. Rhabdoid Tumors Are Sensitive to the Protein-Translation Inhibitor Homoharringtonine. Clinical Cancer Research, 2020; 26:4995-5006.

<u>Complete List of Published Work in MyBibliography:</u>

http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/43572985/?sort=date&direction=ascending