BIOGRAPHICAL SKETCH

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NAME: Zhang, Weizhou

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

POSITION TITLE: Associate Professor

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)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
Nankai University, Tianjin, China	BS	08/1994	07/1998	Microbiology
Institute of Microbiology, CAS, Beijing, China	MS	08/1998	07/2001	Microbiology
Mount Sinai School of Medicine, NY, NY	PhD	09/2001	10/2006	Microbiology
University of California, San Diego, CA	Postdoc	06/2007	07/2012	Pharmacology

A. Personal Statement

The laboratory has focused on two major projects: **1)** how epithelial cell-intrinsic signaling pathways are altered during cancer development. Our earlier research defines two different populations of cell-of-origins for HER2-induced breast cancer, from both luminal and basal mammary epithelial cells (PMID: 23602409, *Cancer Cell*, 2013). We identified a paracrine regulation within different mammary lineages, from luminal WNT-5A production to the inhibition of basal tumor-initiating cells in the HER2-induced breast cancer (*reference 1*). We continue to understand the functions of different WNT ligands and receptors in mammary gland biology and breast cancer; **2)** how tumor immune microenvironment (TIME) controls or promotes cancer under different pathological or therapeutic conditions. This project defines a unique interaction between obesity and cancer progression by stimulating NLRC4 inflammasome activation and interleukin-1β production within the tumor-associated macrophages (TAMs) (*reference 2*). We continue to understand how NLRC4 inflammasome is selectively activated under obesity and how interleukin-1β passes obesity-specific signals to neoangiogenesis in cancer. Along this line, we found that interleukin-1β induces a strong production of ANGPTL4 from adipocytes, resulting in the obesity-associated neoangiogenesis (PMID: 30518876, *Oncogene*. 2019). We have developed and filled a patent on several antibodies that target human ANGPTL4 for anti-angiogenesis therapy.

To understand the complexity of TIME, we started a project on single cell RNA sequencing of human cancer-infiltrating immune cells from renal cancer specimens. In addition to paint a clear picture of RCC immune landscape, we decide to focus on the role of human tumor-infiltrating regulatory T cells (Tregs), a long-standing interest in our laboratory (PMID: 21326202, *Nature*. 2011). Using our single-cell dataset, we were able to identify two most distinct and targetable molecules including CD177 (*reference 3*) and BCL-X_L (*reference 4*). We are also developing novel cancer immunotherapies using Proteolysis-targeting chimeras (PROTAC) to target several intracellular proteins including BCL-XL, NR4A1 and several others.

Ongoing and recently completed projects that I would like to highlight include:
W81XWH2110004
Zhang (PI)
01/01/21-12/31/23
Developing a Novel PROTAC-Based NR4A1 Degrader for Breast Cancer Therapy

W81XWH-19-1-0059
Zhang (PI)
04/01/19-03/31/22
Modulating Cancer Genetics for Immune Regulation and Breast Cancer Therapy

R01CA200673
Zhang (PI)
12/07/15-11/30/21
Obesity, inflammation and breast cancer

AGR DTD 12/1/20
Zhang (PI)
12/01/20-11/30/21
Sanofi 2020 iAwards

R01CA260239
Zhang (PI)
04/01/21-04/30/26
Proteolysis-targeting chimera against BCL-XL inhibits breast cancer metastasis

R01CA203834
Zhang (PI)
03/14/19-06/30/22
CD177 suppresses breast-cancer development by inhibiting beta-catenin

Citations:

1. Borcherding N, Kusner D, Kolb R, Xie Q, Li W, Yuan F, Velez G, Askeland R, Weigel RJ, **Zhang W**. Paracrine WNT5A Signaling Inhibits Expansion of Tumor-Initiating Cells. Cancer Res. 2015 May 15;75(10):1972-82. PMCID: PMC4433621.
2. Kolb R, Phan L, Borcherding N, Liu Y, Yuan F, Janowski AM, Xie Q, Markan KR, Li W, Potthoff MJ, Fuentes-Mattei E, Ellies LG, Knudson CM, Lee MH, Yeung SJ, Cassel SL, Sutterwala FS, **Zhang W**. Obesity-associated NLRC4 inflammasome activation drives breast cancer progression. Nat Commun. 2016 Oct 6;7:13007. PMCID: PMC5059727.
3. Kim M-C, Borcherding N, Ahmed KK, Voigt AP, Vishwakarma A, Kolb R, Kluz PN, Pandey G, De U, Drashansky T, Helm EY, Zhang X, Gibson-Corley KN, Klesney-Tait J, Zhu Y, Lu JL, Lu JS, Huang X, Xiang HR, Cheng JK, Wang DY, Wang Z, Tang J, Hu JJ, Wang ZT, Liu H, Li MJ, Zhuang HY, Avram D, Zhou D, Bacher R, Zheng SG, Wu X, Zakharia Y, **Zhang W**. CD177 modulates the function and homeostasis of tumor-infiltrating regulatory T cells. Nat Commun. 2021 Oct 1;12(1):5764. PMID: 34599187. PMCID: PMC8486774.
4. Kolb R, De U, Khan S, Luo Y, Kim M-C, Yu HJ, Wu CY, Mo J, Zhang X, Zhang PY, Zhang X, Borcherding N, Koppel D, Fu YX, Zheng SG, Avram D, Zheng G, Zhou D, **Zhang** W**.** Proteolysis-targeting chimeras against BCL-XL destroy tumor-infiltrating regulatory T cells. Nat Commun. 2021 Feb 24;12(1):1281. PMID: 33627663. PMCID: PMC7904819.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

10/2021-09/2025	NIH/NCI, Tumor Microenvironment (TME) study section, formal member.
10-12/2021	American Cancer Society, Cancer Health Equity Research Center Minority Serving Institutions, Scientific Reviewer
11/2021	CDMRP/DOD, Breast Cancer Research Program, scientific reviewer
06/2021	NIH/NCI P01 review panel, 06/2021
02/2021	NIH/NCI, Tumor Microenvironment (TME) study section, DC. Ad Hoc. 02/24-25/2021
10/2020	NIH/NCI P01 review panel, Ad Hoc, 09/24-25/2020
2019 – Present	Dr. and Mrs. James Robert Spencer Professor of Pathology, Univ. of Florida, Gainesville, FL
2019	Ad Hoc Scientific Reviewer, NIH/NCI, Tumor Microenvironment Study Section (TME)
2019	NIH/NCI, Beau Biden Cancer Moonshot, Immuno-Oncology Translational Network (IOTN), U01/UG3/UH3
2018 – Present	Associated Professor with Tenure, University of Florida, Gainesville, FL

2018	Ad Hoc Scientific Reviewer, Israel Science Foundation, Individual Research Grants
2018	Ad Hoc Scientific Reviewer, NIH/NCI, Tumor Microenvironment Study Section (TME)
2018	Ad Hoc Scientific Reviewer, Swiss National Science Foundation, Project funding in biology and medicine (division III)
2017 – 2018	Associated Professor with Tenure, Univ. of Iowa/Carver College of Medicine, Iowa City, IA
2017 – 2018	Co-Leader, Cancer Genome and Pathways program, Holden Comprehensive Cancer Center, University of Iowa
2017 – 2018	Co-Leader, Breast Cancer Research Group, Holden Comprehensive Cancer Center, University of Iowa
2017 – 2018	Meeting Organizer, 4th Midwest Tumor Microenvironment Annual Meeting, 2018
2017	Session Chair, Keystone meeting: Cell plasticity within tumor microenvironment
2016	NIH/NCI, Special Emphasis Panel/Scientific Review Group 2017/01 ZCA1 SRB-J (J4) S
2015 – Present	CDMRP/DOD, Breast Cancer Research Program, scientific reviewer
2013 – 2018	Section editor of Oncology, AIMS Medical Sciences
2012 – 2018	Member, Holden Comprehensive Cancer Center, University of Iowa
2012 – 2017	Tenure-track Assistant Professor, Univ. of Iowa/Carver College of Medicine, Iowa City, IA
2009 – 2010	Member, American Society of Hematology
2008 – Present	Full member, American Association for Cancer Research
2007 – 2012	Post-doctoral fellow, University of California, San Diego, CA
2006 – 2007	Post-doctoral fellow, Mount Sinai School of Medicine, New York, NY
2001 – 2006	Graduate Student, Mount Sinai School of Medicine, New York, NY
1998 – 2001	Graduate Student, Institute of Microbiology, Chinese Academy of Sciences, Beijing, China

Honors

2019 – Present	Dr. and Mrs. James Robert Spencer Professor of Pathology, Univ. of Florida, Gainesville, FL
2014 – 2016	The V Scholar Award, from The V Foundation for Cancer Research
2011 – 2015	NIH Pathway to independence award (K99/R00), from National Cancer Institute
2008 – 2011	Postdoctoral Fellowship Award, from the Susan G. Komen for the Cure
2006 – 2007	Postdoctoral Fellowship Award, Health Research Science Board of New York State DOH
2001	Liu Yong-Lin Scholarship for Excellence in Scientific Res. Chinese Academy of Sciences
2001	Outstanding Graduate with Award of Top One Scholarship in the Institute of Microbiology, Chinese Academy of Sciences, China
1998	Outstanding Graduate from the Nankai University

C. Contributions to Science

1. We are interested in the role of TNF super family in cancer. We have developed two novel mouse models for human chronic lymphocytic leukemia, the most prevalent leukemia in western countries. We found that microenvironmental BAFF secretion likely from nurse-like cells promotes CLL development (a,b). I am also involved in a distinct regulatory mechanism downstream of CD40 receptor (c)..
    a. *Enzler T, *****Kater AP, ***Zhang W**, Widhopf GF 2nd, Chuang HY, Lee J, Avery E, Croce CM, Karin M, Kipps TJ. Chronic lymphocytic leukemia of Emu-TCL1 transgenic mice undergoes rapid cell turnover that can be offset by extrinsic CD257 to accelerate disease progression. Blood. 2009 Nov 12;114(20):4469-76. Erratum in: Blood. 2010 Jul 29;116(4):671. (*equal contribution).
    b. **Zhang W**, Kater AP, Widhopf GF 2nd, Chuang HY, Enzler T, James DF, Poustovoitov M, Tseng PH, Janz S, Hoh C, Herschman H, Karin M, Kipps TJ. B-cell activating factor and v-Myc myelocytomatosis viral oncogene homolog (c-Myc) influence progression of chronic lymphocytic leukemia. Proc Natl Acad Sci U S A. 2010 Nov 2;107(44):18956-60. PMCID: PMC2973856.
    c. Matsuzawa A, Tseng PH, Vallabhapurapu S, Luo JL, **Zhang W**, Wang H, Vignali DA, Gallagher E, Karin M. Essential cytoplasmic translocation of a cytokine receptor-assembled signaling complex. Science. 2008 Aug 1;321(5889):663-8. PMCID: PMC2669719.

2. We have also focused on how tumor immune microenvironment (TIME) promote cancer progression under the comorbid obesity. We identified a unique activation of macrophages in obesity-associated tumor microenvironment by activating NLRC4 inflammasome and IL-1β (a). We further found IL-1β induces the production of angiopoietin like 4 (ANGPTL4) within TIME, leading to obesity-induced angiogenesis (b). We recently developed several anti-c-terminal ANGPTL4 (human) antibodies that have been patented (c).

a. Kolb R, Phan L, Borcherding N, Liu Y, Yuan F, Janowski AM, Xie Q, Markan KR, Li W, Potthoff MJ, Fuentes-Mattei E, Ellies LG, Knudson CM, Lee MH, Yeung SJ, Cassel SL, Sutterwala FS, **Zhang W**. Obesity-associated NLRC4 inflammasome activation drives breast cancer progression. Nat Commun. 2016 Oct 6;7:13007. PMCID: PMC5059727.
b. Kolb R, Kluz P, Tan ZW, Borcherding N, Bormann N, Vishwakarma A, Balcziak L, Zhu P, Davies BS, Gourronc F, Liu LZ, Ge X, Jiang BH, Gibson-Corley K, Klingelhutz A, Tan NS, Zhu Y, Sutterwala FS, Shen X, **Zhang W**. Obesity-associatedinflammation promotes angiogenesis and breast cancer via angiopoietin-like 4. Oncogene. 2019 Mar;38(13):2351-2363. PMCID: PMC6440811.
c. **Weizhou Zhang** & Ryan Kolb, inventors; University of Florida Research Foundation, Incorporated, assignee. Anti-angiopoietin-like 4 (ANGPTL-4) antibodies and methods of use. United States Patent US 62/927289. 2019 Oct 29.

3. We have been interested in studying the paracrine signaling between luminal epithelial cells and basal epithelial cells in the mammary gland during carcinogenesis. Our work defined the alternative NF-κB activation within the basal compartment, which is critical to promote the expansion of basal tumor initiating cells via suppression p27/Kip1 (a). The activation of alternative NF-κB activation within basal compartment likely is mediated by the luminal RANKL or other TNF family members. We have defined a paracrine suppressive signaling flow from luminal WNT-5A production to the suppression of basal cell expansion via RYK receptor (b). ROR1-another WNT-5A receptor-is not important for mediating WNT-5A signaling, rather inducing a tumor-promoting signaling network via the regulation of fibroblast growth factor receptor (FGFR) in basal like breast cancer (c). Along the same line of WNT signaling, we also found that the structural E-Cadherin and β-Catenin protein expression in adherens junctions is critical in predicting a bad prognosis of breast cancer, rather than the commonly believed WNT-β-Catenin activation (d).
   a. **Zhang W**, Tan W, Wu X, Poustovoitov M, Strasner A, Li W, Borcherding N, Ghassemian M, Karin M. A NIK-IKKα module expands ErbB2-induced tumor-initiating cells by stimulating nuclear export of p27/Kip1. Cancer Cell. 2013 May 13;23(5):647-59. PMCID: PMC3981467.
   b. Borcherding N, Kusner D, Kolb R, Xie Q, Li W, Yuan F, Velez G, Askeland R, Weigel RJ, **Zhang W**. Paracrine WNT5A Signaling Inhibits Expansion of Tumor-Initiating Cells. Cancer Res. 2015 May 15;75(10):1972-82. PMCID: PMC4433621.
   c. Pandey G, Borcherding N, Kolb R, Kluz P, Li W, Sugg S, Zhang J, Lai DA, **Zhang W**. ROR1 Potentiates FGFR Signaling in Basal-Like Breast Cancer. Cancers (Basel). 2019 May 24;11(5):718. PMCID: PMC6562526.
   d. Borcherding N, Cole K, Kluz P, Jorgensen M, Kolb R, Bellizzi A, **Zhang W**. Re-Evaluating E-Cadherin and β-Catenin: A Pan-Cancer Proteomic Approach with an Emphasis on Breast Cancer. Am J Pathol. 2018 Aug;188(8):1910-1920. PMCID: PMC6119824.

4. Our recent effort has been to develop bioinformatics analysis and tools in cancer research. Recently, we have revisited E-Cadherin and β-Catenin proteins in breast cancer using bioinformatics tools (a). We made an observation that β-Catenin protein level based on reverse phase protein array and mass spectrometry is a good prognostic factor in breast cancer (a). We further expanded upon this study to develop an online tool for using the Cancer Protein Atlas to predict patient outcome (b). Recently, we have matured the analysis of single cell RNAseq and found heterogeneity within cutaneous T cell lymphoma (c) and finished building up an Immune Landscape of Clear Cell Renal Cell Carcinoma by Single-Cell RNA-seq (d).
   a. Borcherding N, Cole K, Kluz P, Jorgensen M, Kolb R, Bellizzi A, **Zhang W**. Re-Evaluating E-Cadherin and β-Catenin: A Pan-Cancer Proteomic Approach with an Emphasis on Breast Cancer. Am J Pathol. 2018 Aug;188(8):1910-1920. PMCID: PMC6119824.
   b. Borcherding N, Bormann NL, Voigt AP, **Zhang W**. TRGAted: A web tool for survival analysis using protein data in the Cancer Genome Atlas. F1000Res. 2018 Aug 10;7:1235. PMCID: PMC6173115.
   c. Borcherding N, Voigt AP, Liu V, Link BK, **Zhang W**, Jabbari A. Single-Cell Profiling of Cutaneous T-Cell Lymphoma Reveals Underlying Heterogeneity Associated with Disease Progression. Clin Cancer Res. 2019 May 15;25(10):2996-3005. PMCID: PMC6659117.
   d. Borcherding N, Vishwakarma A, Chimenti MS, Vishwakarma P, Nepple K, Salem A, Jenkins RW*, Zakharia Y*, **Zhang W***. Mapping the Immune Landscape of Clear Cell Renal Cell Carcinoma by

Single-Cell RNA-seq. 2021. *Communications Biology.* 2021 Jan 27;4(1):122. PMID: 33504936; PMCID: PMC7840906.

5. We have a long-standing interest in understanding tumor-infiltrating regulatory T cells. Our earlier work defines a direct contribution of tumor-infiltrating Tregs in promoting pulmonary metastasis via RANKL production (a). We have recently gained interest in another human cancer Treg marker, namely CD177 that mediates several distinct functions in TIME. Our established CD177 genetic knockout mice did not exhibit significant phenotypic change under physiological condition or bacterial infections (b). In TIME, however, CD177 has two distinct mechanisms. One mechanism is related to the epithelial cell-function of CD177 where we found that CD177 has a tumor-suppressive function by attenuating β-Catenin-mediated signaling transduction (c). The 2nd mechanism is related to its expression on human cancer Tregs. We found that all solid tumor-infiltrating Tregs have 20% with CD177 expression on their surface, a population that mediates Treg suppressive activity and can be blocked by anti-CD177 antibody (d).
    a. *Tan W, ***Zhang W**, Strasner A, Grivennikov S, Cheng JQ, Hoffman RM, Karin M. Tumour-infiltrating regulatory T cells stimulate mammary cancer metastasis through RANKL-RANK signalling. Nature. 2011 Feb 24;470(7335):548-53. PMCID: PMC3166217. (*equal contribution)
    b. Xie Q, Klesney-Tait J, Keck K, Parlet C, Borcherding N, Kolb R, Li W, Tygrett L, Waldschmidt T, Olivier A, Chen S, Liu GH, Li X, **Zhang W**. Characterization of a novel mouse model with genetic deletion of CD177. Protein Cell. 2015 Feb;6(2):117-26. PMCID: PMC4312768.
    c. Kluz PN, Kolb R, Xie Q, Borcherding N, Liu Q, Luo Y, Kim MC, Wang L, Zhang Y, Li W, Stipp C, Gibson-Corley KN, Zhao C, Qi HH, Bellizzi A, Tao AW, Sugg S, Weigel RJ, Zhou D, Shen X, **Zhang W**. Cancer cell-intrinsic function of CD177 in attenuating β-catenin signaling. Oncogene. 2020 Apr;39(14):2877-2889. PMCID: PMC7127950.
    d. Kim M-C, Borcherding N, Ahmed KK, Voigt AP, Vishwakarma A, Kolb R, Kluz PN, Pandey G, De U, Drashansky T, Helm EY, Zhang X, Gibson-Corley KN, Klesney-Tait J, Zhu Y, Lu JL, Lu JS, Huang X, Xiang HR, Cheng JK, Wang DY, Wang Z, Tang J, Hu JJ, Wang ZT, Liu H, Li MJ, Zhuang HY, Avram D, Zhou D, Bacher R, Zheng SG, Wu X, Zakharia Y, **Zhang W**. CD177 modulates the function and homeostasis of tumor-infiltrating regulatory T cells. *Nat Commun.* 2021 Oct 1;12(1):5764. PMID: 34599187. PMCID: PMC8486774.

6. Our current effort has been extended to drug development field in collaborations with other groups. We have been targeting BCL-XL, CD177 and several other targets for cancer therapy/immunotherapy using either antibody-based or proteolysis targeting chimera (PROTAC) technology. We have used a recently developed BCL-XL PROTACs (a,b) and showed that BCL-XL depletion by PROTAC leads to the activation of anti-cancer immunity (c). We recently patented a series of PROTACs that leads to the degradation of NR4A1 for cancer immunotherapy (d).
    a. Khan S, Zhang X, Lv D, Zhang Q, He Y, Zhang P, Liu X, Thummuri D, Yuan Y, Wiegand JS, Pei J, **Zhang W**, Sharma A, McCurdy CR, Kuruvilla VM, Baran N, Ferrando AA, Kim YM, Rogojina A, Houghton PJ, Huang G, Hromas R, Konopleva M, Zheng G, Zhou D. A selective BCL-XL PROTAC degrader achieves safe and potent antitumor activity. Nat Med. 2019 Dec;25(12):1938-1947. PMID: 31792461 PMCID: PMC6898785.
    b. Lv D, Pal P, Liu X, Jia Y, Thummuri D, Zhang P, Hu W, Pei J, Zhang Q, Zhou S, Khan S, Zhang X, Hua N, Yang Q, Arango S, **Zhang W**, Nayak D, Olsen SK, Weintraub ST, Hromas R, Konopleva M, Yuan Y, Zheng G, Zhou D. Development of a BCL-xL and BCL-2 dual degrader with improved anti-leukemic activity. Nat Commun. 2021 Nov 25;12(1):6896. PMID: 34824248 PMCID: PMC8617031
    c. Kolb R, De U, Khan S, Luo Y, Kim M-C, Yu HJ, Wu CY, Mo J, Zhang X, Zhang PY, Zhang X, Borcherding N, Koppel D, Fu YX, Zheng SG, Avram D, Zheng G, Zhou D, **Zhang W.** Proteolysis-targeting chimeras against BCL-XL destroy tumor-infiltrating regulatory T cells. Nat Commun. 2021 Feb 24;12(1):1281. PMID: 33627663. PMCID: PMC7904819.
    d. **Weizhou Zhang**, Guangrong Zheng, Daohong Zhou, Yufeng Xiao & Lei Wang, inventors; University of Florida Research Foundation, Incorporated, assignee. Modulators of nuclear receptor subfamily 4 group a member 1 (nr4a1) and uses thereof. International Patent PCT/US21/48007/US 63/071733. 08/27/2021

Complete List of Published Work in MyBibliography (85 total citations):
https://www.ncbi.nlm.nih.gov/myncbi/weizhou.zhang.1/bibliography/public/