BIOGRAPHICAL SKETCH

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NAME: Wang, Rongfu

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

POSITION TITLE: Professor of Medicine and Pediatrics, Director of Cell Immunotherapy, CHLA/USC

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
Zhejiang University, Zhejiang, P.R. China	B.S	07/1982	Biology
The Institute of Genetic and Physiology, Nanjing, P. R China	M.S	07/1984	Biochemistry
The University of Georgia	Ph.D	03/1992	Molecular Genetics
Stanford University, Palo Alto, CA	Postdoc	03/1994	Immunology/Virology

A. Personal Statement

My research interests include cancer antigen discovery, cancer immunology and immunotherapy, innate immune signaling and regulation, epigenetic regulation of stem cells and cancer. My group has identified many tumor antigens, including NY-ESO-1, LAGE1, DRG-1, TRP1 and TRP2 that are recognized by $CD4^+$ and $CD8^+$ T cells. My group also developed a genetic targeting expression system to identify many neoantigens (CDC27, TPI, Fibronectin and fusion antigen) recognized by antigen-specific $CD4^+$ T cells derived from cancer tissues. In particular, NY-ESO-1-specific T cell receptor (TCR) engineered T cell therapy has shown 55% of clinical response rate. As one of most immunogenic antigens recognized by T cells and antibodies, NY-ESO-1 is highly expressed in several types of cancers, including breast cancer, but not on normal tissues, thus serving a potential therapeutic target. Specifically, we found that 30% of primary triple-negative breast cancer samples collected from patients expressed NY-ESO-1. Further studies demonstrated that HLA-DP4-restricted NY-ESO-1 TCR-engineered $CD4^+$ T cells inhibited tumor growth in NSG mice. My team is currently testing the safety and clinical efficacy of NY-ESO-1 TCR-T cell immunotherapy in breast cancer. Regulatory T cell-mediated immune suppression at tumor sites, at least in part, explains why current immunotherapies fail to persistently produce a therapeutic effect. To overcome immune suppression in the tumor microenvironment, my group shows that Toll-like receptor (TLR8) signaling is essential in reversing Treg cell suppressive function. Further studies demonstrated that innate immune signaling could modulate Treg cell function. Further understanding of the mechanisms of cellular reprogramming will lead to the development of novel cancer therapeutics. Vaccination with antigenic peptides or dendritic cells (DCs) pulsed with antigenic peptides can generate antitumor immunity, but so far, these vaccine studies have met with only sporadic clinical success. I am developing novel strategies to improve vaccine-based immunotherapy with minimal side effects using nanotechnology-based approaches. My laboratory recently completed a phase I clinical trial, which we demonstrated that NY-ESO-1 peptide vaccines safely elicit tumor- specific immunity and increased prostate specific antigen doubling time in prostate cancer patients. My long-term goals are to understand mechanisms of antitumor immunity and tolerance, and to develop therapeutics that will significantly impact public health. I have extensive experience in administrating research projects, supervising co-investigators (staffs, students and postdoctoral fellows), collaborating with other researchers and publishing high quality peer-reviewed papers. The research activities represent my long-term interests and experts in cancer antigen discovery, neoantigen-specific personalized vaccines, and TCR/CAR-T cell immunotherapy.

1. **Wang RF**, Wang X, Atwood AL, Topalian SL, and Rosenberg SA. 1999. Cloning genes encoding MHC class II-restricted antigens: mutated human CDC27 as a tumor antigen. ***Science*** 284, 1351-1354. PMID: 10334988.

2. Zeng G, Wang X, Robbins PF, Rosenberg Sa, and **Wang RF**. 2001. $CD4^+$ T cell recognition of MHC class II-restricted epitopes from NY-ESO-1 presented by a prevalent HLA DP4 allele: Association with NY- ESO-1 antibody production. ***Proc Natl Acad Sci USA*** Mar 27:98(7):3964-9. PMID: 11259659. PMCID: PMC31162.
3. Peng G, Guo Z, Kiniwa Y, Voo KS, Peng W, Fu T, Wang DY, Li Y, Wang HY, and **Wang RF**. 2005. Toll-like receptor 8 mediated-reversal of $CD4^+$ regulatory T cell function. ***Science*** 309; 380-1384. PMID: 16123302.
4. Sonpavde G, Wang M, Peterson LE, Wang HY, Joe T, Mims MP, Kadmon D, Ittmann MM, Wheeler TM, Gee AP, **Wang RF***, and Hayes TG. (* Co-corresponding authors). 2014. HLA-restricted NY-ESO-1 peptide immunotherapy for metastatic castration resistant prostate cancer. ***Invest New Drugs*** 32: 235-242. PMID: 23609828. PMCID: PMC4100683.
5. Zhao W, Li Qingtian, Ayers S, Gu Y, Shi Z, Zhu Q, Chen Y, Wang HY, and **Wang RF**. 2014. Jimjd3 inhibits Reprogramming by upregulating expression of *INK4a/Arf* and targeting PHF20 for Ubiquitination. ***Cell*** 152, 137 150. PMID: 23452852. PMCID: PMC3742052.

B. Positions and Honors

Positions and Employment

1992 – 1993	Postdoctoral Fellow, Immunology, Stanford University Medical School, CA.
1994 – 1995	Research Fellow, National Cancer Institute, Bethesda, MD
1996 – 2000	Senior Investigator, National Cancer Institute, Bethesda, MD
2000 – 2004	Associate Professor, Baylor College of Medicine, Houston, TX
2004 – 2011	Professor, Baylor College of Medicine, Houston, TX
2007 – 2011	Jack L. Titus Professor of Immunology, Baylor College of Medicine, Houston, TX
2011 – present	Director and Senior Member, Center of Inflammation and Epigenetics, the Methodist Hospital Research Institute, Houston, TX.
2011 – present	Professor, Microbiology and Immunology, Weill Cornell Medicine, Cornell University, NY.

Other Experience and Professional Memberships

Member, American Society of Immunology
Member, AACR
Reviewer, UK government and Wellcome Trust Joint Foundation
NIH study section, Experimental Immunology
NIH study section, Cancer Immunology and Immunotherapy

Honors

1992	Distinguished dissertation, University of Georgia
1996	Recipient of NIH Fellows Award for Research Excellence
1999-2000	Intramural Research Award, NCI
2000	Outstanding Young Scientist Award
2003	American Cancer Society Research Scholar
2006	The Michael DeBakey Excellence in Research Award, Baylor College of Medicine
2007-2011	Jack L. Titus Professorship at BCM
2013	President's Award for transformative excellence, HMRI
2016	President's Award for transformative excellence, HMRI
2016	Award for Excellence in Transformative Research, HMRI, 2016.

C. Contribution to Science

1. Tumor Antigen Discovery and Cancer Immunotherapy

I have identified several important cancer antigens that are recognized by T cells, which has led to the development of effective immunotherapies for cancer patients. NY-ESO-1 as one of the most immunogenic antigens recognized by T cells and antibodies derived from cancer patients. I am the first to develop a genetic targeting expression system that allows one to identify many MHC class II-restricted mutated tumor antigens or neoantigens recognized by tumor-reactive CD4+ and CD8+ T cells. Combination of whole exome sequencing and targeting expression system permits rapid identification of neoantigens derived from somatic mutations for developing vaccines and T-cell immunotherapy.

a) Wang RF, Wang X, Atwood AL, Topalian SL, and Rosenberg SA. 1999. Cloning genes encoding MHC class II-restricted antigens: mutated human CDC27 as a tumor antigen. Science 284, 1351-1354. PMID: 10334988.

b) Wang RF and Wang HY. 2002. Enhancement of antitumor immunity by prolonging antigen presentation on dendritic cells. Nat Biotechnol. 20: 149-154. PMID: 11821860.

c) Wang HY, Zhou J, Zhu K, Marincola FM, and Wang RF. 2002. Identification of a mutated fibronectin as a tumor antigen recognized by CD4+ T cells: its role in extracellular matrix formation and tumor metastasis. J. Exp. Med. 195: 1397-1406. PMID: 12045238

d) Xia, X., Mai, J., Xu, R., Perez, J.E., Guevara, M.L., Shen, Q., Mu, C., Tung, H.Y., Corry, D.B., Evans, S.E., Liu, X., Ferrari, M., Zhang, Z., Li, X.C., Wang, R.F. & Shen, H. 2015. Porous Silicon Microparticle Potentiates Anti-Tumor Immunity by Enhancing Cross-Presentation and Inducing Type I Interferon Response. Cell Rep 11, 957-966. PMID:25937283

e) Wang R.F, Wang HY. Immune targets and neoantigens for cancer immunotherapy and precision medicine. *Cell Res* 2017; 27:11-37. PMID:28025978

f) Zhu, M., Ding, X., Zhao, R., Liu, X., Shen, H., Cai, C., Ferrari, M., Wang, H.Y. & Wang, R.F. (2018). Co-delivery of tumor antigen and dual toll-like receptor ligands into dendritic cell by silicon microparticle enables efficient immunotherapy against melanoma. *J Control Release* 272, 72-82.PMID:29325699

2. Regulatory T cells in Tumor Microenvironment. Regulatory T cells (Treg) cells play a crucial role in maintaining immune homeostasis and self-tolerance. My team showed the presence of tumor-specific CD4+ Treg cells in cancer-derived tumor-infiltrating lymphocytes. Treg-mediated immune suppression at tumor sites may, at least in part, explain why current cancer vaccines induce only weak and transient immune responses and fail to produce therapeutic benefit. My laboratory has found that human Toll-like receptor (TLR) 8 reverses Treg cell function upon stimulation by it ligand, Poly-G3 oligonucleotide. The use of TLR8 ligands to overcome Treg-mediated immune suppression may offer new opportunities to improve the outcome of cancer immunotherapy.

a) Wang HY, Lee DA, Peng G, Guo Z, Li Y, Kiniwa Y, Shevach EM, and Wang RF. 2004. Tumor-specific human CD4+ regulatory T cells and their ligands: implication for immunotherapy. Immunity 20:107-118. PMID: 14738769.

b) Peng G, Guo Z, Kiniwa Y, Voo KS, Peng W, Fu T, Wang DY, Li Y, Wang HY, and Wang RF. 2005. Toll-like receptor 8 mediated-reversal of CD4+ regulatory T cell function. Science 309; 380-1384. PMID: 16123302.

c) Peng G, Wang HY, Peng W, Kiniwa Y, Seo KH, and Wang RF. 2007. Tumor-infiltrating gammadelta T cells and their regulatory suppressive mechanisms controlled by a unique TLR signaling pathway. Immunity 27: 334-348. PMID: 17656116.

d) Miyahara Y, Odunsi K, Chen W, Peng G, Matszaki J, and Wang RF. 2008. Generation and regulation of human CD4+ IL-17-producing T cells in ovarian cancer. Proc Natl Acad Sci USA 105(40):15505-10. PMID: 18832156.

3. Innate Immune Signaling. Innate immune signaling protects hosts from pathogens and modulates adaptive immune responses. We have identified several novel negative regulators (NLRC5, NLRX1, and NLRP4) that control NF-kB and type I interferon pathways and inflammation. Increasing evidence suggests that inflammation induced by invading pathogens is a major driving force in the control or promotion of cancer development, and my group has defined a role for TAK1 in inflammation and colon cancer. Our research will lead to better understanding of innate immune signaling and the development of more successful malaria vaccines and cancer vaccines.

a) Cui J, Zhu L, Xia X, Wang HY, Legras X, Hong J, Ji J, Shen P, Zheng S, Chen ZJ, and Wang RF. 2010. NLRC5 negatively regulates the NF-κB and type I interferon signaling pathways. Cell 141:483-496. PMID: 20434986.

b) Xia X, Cui J, Wang HY, Zhu L, Matsueda S, Wang Q, Yang X, Hong J, Songyang Z, Chen Z, and Wang RF. 2011. NLRX1 negatively regulates TLR-induced NF-κB signaling by targeting TRAF6 and IKK. Immunity 34, 843-853. PMID: 21703539.

c) Ajibade A, Wang Q, Cui J, Zou J, Xia X, Wang M, Tong Y, Hui W, Liu D, Su B, Wang HY and Wang RF. 2012. TAK1 negatively regulates NF-κB and p38 MAPK activation in Gr-1+CD11b+ neutrophils. Immunity 36, 43-54. PMID: 22226633.

d) Cui J, Li Y, Zhu L, Liu D, Songyang Z, Wang HY & Wang RF. 2012. NLRP4 negatively regulates type I interferon signaling by targeting the kinase TBK1 for degradation via the ubiquitin ligase DTX4. Nat Immunol. 13, 387-395. PMID: 22388039.

e) Xiao Yu, Baowei Cai, Mingjun Wang, Peng Tan, Xilai Ding, Jian Wu, Jian Li, Qingtian Li, Pinghua Liu, Changsheng Xing, Helen Y. Wang, Xin-zhuan Su, and Rong-Fu Wang. (2016). Cross-regulation of two type I interferon signaling pathways in plasmacytoid dendritic cells controls the protective immunity against lethal malaria YM infection. Immunity, 45:1093-1107. PMID:27793594

4. Epigenetic Reprogramming of iPSCs, Cancer and Immune cells. Induced pluripotent stem cells hold great promise for tissue regeneration, disease modeling, and drug screening. However, the generation of these cells is inefficient, which is due, in part, to epigenetic barriers. My team characterized Jmjd3 as a potent negative epigenetic regulator of somatic cell reprogramming. This research has led to the identification of the role of Jmjd3 in cancers, such as kidney, glioma, neuroblastoma, leukemia, colon, and lymphoma. Furthermore, my group found that Jmjd3 also regulates T cell differentiation, specifically CD4+ T cell-polarization into several subtypes. Dysregulation of CD4+ T cell-differentiation is associated with various autoimmune and inflammatory diseases such as myelodysplastic syndromes and systemic lupus erythematosus. My research contributes to a better understanding of cellular reprogramming, which may lead to more efficient strategies for iPSC generation, to cancer therapeutics, and to the clinical development of modulators of T cell differentiation.

a) Zhao W, Li Qingtian, Ayers S, Gu Y, Shi Z, Zhu Q, Chen Y, Wang HY, and Wang RF. 2014. Jimjd3 inhibits Reprogramming by upregulating expression of INK4a/Arf and targeting PHF20 for Ubiquitination. Cell 152, 137-150. PMID: 23452852.

b) Li Q, Wang HY, Chepelev I, Zhu Q, Wei G, Zhao K, and Wang RF. 2014. Stage-Dependent and Locus-Specific Role of Histone Demethylase Jumonji D3 (Jmjd3) in the Embryonic Stages of Lung Development. PLoS Genet. Jul; 10(7). PMID:25079229.

c) Li, Q., Zou, J., Wang, M., Ding, X., Chepelev, I., Zhou, X., Zhao, W., Gang, W., Cui, J., Zhao, K., Wang, H.Y., and Wang-R.F. 2014. Critical role of histone demethylase Jmjd3 in the regulation of CD4+ T-cell differentiation. Nat Commun. Dec 22;5:5780. PMID:25531312.

d) Burchfield, J.S., Li, Q., Wang, H.Y. & Wang, R.F. JMJD3 as an epigenetic regulator in development and disease. Int J Biochem Cell Biol 67, 148-157 (2015). PMID:26193001

e) Ning, B., Li, W., Zhao, W. & Wang, R. F. Targeting epigenetic regulations in cancer. Acta Biochim Biophys Sin (Shanghai) 48, 97-109 (2016). PMID:26508480

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1v96ypUm8xc5E/bibliography/48077601/public/?sort=date&direction=ascending