BIOGRAPHICAL SKETCH

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NAME: Zhang, Yanping

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

POSITION TITLE: Professor of Cancer Biology

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
Fudan University, Shanghai, China	B.S.	09/1982	Microbiology
Fudan University, Shanghai, China	M.S.	09/1985	Virology
University of Nebraska, Lincoln, Nebraska	Ph.D.	01/1992	Molecular Biology

A. Personal Statement

The broad goal of my research is to uncover the complex regulatory network surrounding the MDM2/MDMX-p53 tumor suppression pathway, thereby providing a possible means to manipulate p53 function. I have the expertise and leadership skills necessary to successfully carry out the proposed programs. Over the past 20-plus years, I have been involved in various important discoveries of the function, mechanism, and regulation of the tumor suppressor p53. Our earlier work discovered the tumor suppressor p14ARF interaction with MDM2, a finding that established the p14ARF-MDM2-p53 signaling pathway. We identified a nuclear export signal sequence in p53 and elucidated the mechanism behind p53 nucleo-cytoplasmic shuttling. We provided the first evidence for ribosomal protein RPL11 interaction with MDM2 and established the RP-MDM2-p53 tumor suppression pathway. Our lab pioneered a paradigm for the *in vivo* function of MDM2 E3 ubiqutin ligase by developing and characterizing several MDM2 point mutation knock-in mouse models, which redefined the function and mechanism of MDM2 E3 ubiquitin ligase. Throughout the years I have proved research capabilities in four areas: *(i)* Identifying and persistently investigating the important questions relevant to p53 signaling and cancer prevention. *(ii)* Combining multi-disciplinary approaches in biomedical research. *(iii)* Demonstrating high enthusiasm and collegiality in collaboration with colleagues at the University of North Carolina at Chapel Hill and across the world. *(iv)* Motivating and nurturing young graduate students and postdoctoral fellows. The research programs outlined in this application are based on our own experimental observations in mice and cell cultures that have suggested previously unexpected roles of the ribosomal protein in the regulation of p53 and its role in ribosomopacy and hematopoietic malignancy. My expertise and experience in related areas have fully prepared me to lead and carry out the proposed researches.

1. Koji Itahana, Hua Mao, Aiwen Jin, Hilary Clegg, Yoko Itahana, Mikael S. Lindström, Krishna P. Bhat, Virginia L. Godfrey, and Yanping Zhang. Targeted inactivation of Mdm2 E3 ubiquitin ligase activity in the mouse reveals novel mechanistic insights into p53 regulation. ***Cancer Cell***, 2007, 12:355–366.

2. Koji Itahana and Yanping Zhang. p32 is a critical mediator of ARF-induced apoptosis. ***Cancer Cell***, 2008, 13:542–553.

3. Everardo Macias, Aiwen Jin, Chad Deisenroth, Krishna Bhat, Hua Mao, Mikael S. Lindström, and Yanping Zhang. An ARF-independent c-Myc-activated tumor suppression pathway mediated by ribosomal protein-Mdm2 interaction. ***Cancer Cell***, 2010, 18(3):231-43.

4. Laura A. Tollini, Aiwen Jin, Jikyoung Park, and Yanping Zhang. Regulation of p53 by Mdm2 E3 Ligase Function is Dispensable in Embryogenesis and Development but Essential in Response to DNA Damage. ***Cancer Cell***, 2014, August. 26, 235–247.

B. Positions and Honors

Positions and Employment

1992-1996	VP and Co-Founder, Megabase Research Products, Lincoln, Nebraska
1997-2000	Postdoctoral Fellow, University of North Carolina at Chapel Hill
2001-2003	Assistant Professor (tenure track), U.T. MD Anderson Cancer Center, Houston, Texas
2004-2005	Assistant Professor (tenure track), University of North Carolina at Chapel Hill
2006-2009	Associate Professor (tenured), University of North Carolina at Chapel Hill
2010-	Professor, University of North Carolina at Chapel Hill

Other Experience and Professional Memberships

1998-	Member of American Association for Cancer Research (AACR)
2000-	Member of American Association for the Advancement of Science (AAAS)
2001-04	Fellow of the M.D. Anderson Research Trust
2001-04	Odyssey Advisory committee (MD Anderson Cancer Center)
2001-	Society of Chinese Bioscientists in America (SCBA)
2005-07	Graduate Admission Committee for Molecular and Genetic Biology (UNC)
2005-06	Reviewer, DOD Breast Cancer Research Program Study Section
2005-	Reviewer, DOD Prostate Cancer Research Grants Program Study Section
2007-	Ad Hoc Reviewer, NIH CAMP Study Section
2008-	Ad Hoc Reviewer, NIH MONC Study Section
2009-	Ad Hoc Reviewer, NIH CE Study Section
2010-	Ad Hoc Reviewer, NIH BMCT Study Section
2014	Ad Hoc Reviewer, NIH R03 & R21 Omnibus Study Section
2015	Reviewer, Site Visit review for the Division of Intramural Research (DIR)
2016	Reviewer, NIH Special Emphasis Panel (SEP) Review R15 (AREA)
2016	Reviewer, NIH P01 Special Emphasis Panel

Honors

1998	Postdoctoral Fellowship, Lineberger Cancer Center UNC at Chapel Hill
2000	Howard Temin Award (K01)
2000	Burroughs Wellcome Fund Career Award in the Biomedical Sciences
2001	M.D. Anderson Research Trust Fund Award
2003	M.D. Anderson Award for Excellence in Education
2006	Junior Research Fellow, UNC
2007	Leukemia & Lymphoma Society Scholar Award
2008	American Cancer Society Research Scholar Award
2008	UNC Jefferson-Pilot Award
2010	The Battle Distinguished Cancer Research Award

C. Contributions to Science

1. Discovered a nuclear export signal in p53 and contributed to understanding of p53 nucleo-cytoplasmic shuttling

We identified a nuclear export signal (NES) sequence in the amino-terminal region of p53 and demonstrated that the serine residues in the N-terminal NES become phosphorylated in response to DNA damage, and the phosphorylation blocked the NES function and trapped p53 in the nucleus, thereby facilitating p53 transcriptional activation. Subsequently, our lab showed that several conserved residues in both the NES and the NLS (nuclear localization signal) of p53 are critically important for regulating p53 nucleo-cytoplasmic shuttling, protein stability and transcriptional activity after cells encounter genotoxic stresses.

a. Yanping Zhang, Yue Xiong. A p53 amino-terminal nuclear export signal inhibited by DNA damage-induced phosphorylation. ***Science***. 2001, 8;292(5523):1910-5.

b. Kevin O'Keefe, Huiping Li, Yanping Zhang. Nucleocytoplasmic shuttling of p53 is essential for MDM2-mediated cytoplasmic degradation but not ubiquitination. ***Mol Cell Biol***. 2003, 23(18): 6396-6405.

c. Yoko Itahana, Edward T. H. Yeh, and Yanping Zhang. Nucleocytoplasmic shuttling modulates activity and ubiquitination-dependent turnover of SUMO-specific protease 2. ***Mol Cell Biol***. 2006, 26(12): 4675-89.

d. Chad Deisenroth, Aaron R Thorner, Takeharu Enomoto, Charles Perou, and Yanping Zhang. Mitochondrial Hep27 is a c-Myb target gene that inhibits Mdm2 and stabilizes p53. ***Mol Cell Biol***, 2010, 30(16):3981-93.

2. Contributed to discovery of the RP-MDM2-p53 signaling pathway

My laboratory was the first to demonstrate ribosomal protein RPL11 interacts with and inhibits the E3 ligase function of MDM2, thereby stabilizing and activating p53. We showed that the RPL11-MDM2 interaction is indispensable for p53 stress response to deregulated ribosomal biosynthesis. By generating the $MDM2^{C305F}$ mutant mice, in which the RPL11-MDM2 interaction is selectively disrupted, we demonstrated that the RPL11-MDM2 interaction is an *in vivo* p53 stress-sensing pathway, which can be activated by aberrant ribosome biogenesis. We showed that the RPL11-MDM2-p53 pathway acts independently of other p53 signaling pathways, including the DNA damage response pathway and the p19ARF-MDM2-p53 oncogenic signaling pathway. Moreover, we have shown that the RPL11-MDM2-p53 pathway is an essential factor for safeguarding against oncogenic c-MYC-induced tumorigenesis, a critical sensor and responder for nutritional status, and a regulator for lipid metabolism. Together, these studies established a new p53 signaling pathway that is mediated by ribosomal protein-MDM2 interaction.

a. Krishna Bhat, Koji Itahana, Aiwen Jin, and Yanping Zhang. Ribosomal protein L11 mediates an MDM2- and p53-dependent ribosomal-stress checkpoint. ***EMBO J***, 2004, 16;23(12): 2402-12.

b. Everardo Macias, Aiwen Jin, Chad Deisenroth, Krishna Bhat, Hua Mao, Mikael S. Lindström, and Yanping Zhang. An ARF-independent c-Myc-activated tumor suppression pathway mediated by ribosomal protein-Mdm2 interaction. ***Cancer Cell***, 2010, 18(3):231-43.

c. Yong Liu, Y izhou He, Aiwen Jin, Andrey P. Tikunov, Lishi Zhou, Laura A. Tollini, Patrick Leslie, Lei O. Li, Rosalind A. Coleman, Jeffrey M. Macdonald, Lee M. Graves, and Yanping Zhang. The RP-Mdm2-p53 pathway coordinates nutrient stress with lipid metabolism by regulating MCD and promoting fatty acid oxidation. ***Proc Natl Acad Sci USA***, 2014 May 28.

d. Shijie Liu, Tae-Hyung Kim, Derek Franklin, and Yanping Zhang. Protection against High-Fat Diet Induced Obesity in $MDM2^{C305F}$ Mice due to Reduced p53 Activity and Enhanced Energy Expenditure. ***Cell Reports***, 2017 Jan 24;18(4):1005-1018.

3. Helped to redefined the dogma of MDM2/MDMX regulation of p53

By generating and examining the $MDM2^{C462A}$ knock-in mice, which lack both MDM2 E3 ligase activity and MDM2-MDMX interaction, and the $MDM2^{Y487A}$ mutant mice, which lack MDM2 E3 ligase activity yet retain MDM2-MDMX interaction, our mouse model studies showed that under unstressed conditions the MDM2-MDMX heterooligomerization, in the absence of E3 ubiquitin ligase activity, is sufficient to suppress p53 to allow normal growth and development. However, upon genotoxic stresses the MDM2 E3 ubiquitin ligase function becomes critical for reducing p53 levels and activity to allow the animals to recovery from the stresses. Our studies also showed that *in vivo* the MDM2 E3 ligase activity is not required for MDM2 itself degradation, a long-held believe that is based on *in vitro* studies, and showed the MDM2 mutants lacking E3 function maintains normal ubiquitination mediated proteasomal degradation.

a. Koji Itahana, Hua Mao, Aiwen Jin, Hilary Clegg, Yoko Itahana, Mikael S. Lindström, Krishna P. Bhat, Virginia L. Godfrey, and Yanping Zhang. Targeted inactivation of Mdm2 E3 ubiquitin ligase activity in the mouse reveals novel mechanistic insights into p53 regulation. ***Cancer Cell***, 2007, 12:355–366.

b. Laura A. Tollini, Aiwen Jin, Jikyoung Park, and Yanping Zhang. Regulation of p53 by MDM2 E3 Ligase function is dispensable in embryogenesis and development but essential in response to DNA damage. ***Cancer Cell***, 2014, 26, 235–247.

c. Patrick L. Leslie, Yanping Zhang. The MDM2 RING and central acidic domains play distinct roles In MDM2 homodimerization and MDM2-MDMX heterodimerization. ***J Biol Chem***, 2015, VOL. 290, NO. 20, pp. 12941–12950.

d. Hui Tian, Nicole R. Tackmann, Aiwen Jin, Junnian Zheng, and Yanping Zhang. Inactivation of the MDM2 RING domain enhances p53 transcriptional activity in mice. ***J Biol Chem***, 2017, 29;292(52):21614-21622. doi: 10.1074/jbc.RA117.000122.

4. Uncovered novel function for p14ARF in the nucleolus and the mitochondria

My lab revealed a new anti tumor function of p14ARF via its binding to and inhibiting the activity of the nucleolar protein nucleophosmin (a.k.a. NPM, B23). We also identified the mitochondrial protein p32 (a.k.a. C1qBP) as a critical mediator of p14ARF's apoptotic function, and demonstrated that the interaction between p14ARF and p32 can be disrupted by human cancer derived mutations specifically targeting the p14ARF C-terminus that is not overlapping with p16.

a. Koji Itahana, Krishna Bhat, Aiwen Jin, Yoko Itahana, David Hawke, Ryuji Kobayashi, and Yanping Zhang. Tumor suppressor ARF degrades B23, a nucleolar protein involved in ribosome biogenesis and cell proliferation. ***Molecular Cell,*** 2003, 12: 1151-64.

b. Koji Itahana and Yanping Zhang. p32 is a critical mediator of ARF-induced apoptosis. ***Cancer Cell***, 2008, 13:542–553.

c. Mikael S. Lindström and Yanping Zhang. Physical and functional interactions between nucleolar B23/NPM and ribosomal protein S9 in cell growth and proliferation. ***J Biol Chem***. 2008, 6;283(23):15568-76.

d. Xuan Meng, Nicole R. Carlso, Jiahong Dong, and Yanping Zhang. Oncogenic c-MYC induced lymphomagenesis is inhibited non-redundantly by the p19ARF-MDM2-p53 and RP-MDM2-p53 pathways. ***Oncogene***, 2015, 30 March 2015; doi: 10.1038.

5. Contributed to establish the p14ARF-MDM2-p53 anti-oncogenic signaling pathway

Our earlier work was the first to demonstrate that the tumor suppressor p14ARF, whose gene is one of the most frequently mutated genes in human cancer, interacts with MDM2 and inhibits MDM2 E3 ligase function, which results in stabilization and activation of p53. This discovery established the so-called p14ARF-MDM2-p53 tumor suppression pathway and fueled intense efforts in the cancer research field to uncover mechanisms involved in oncogene-induced, p14ARF-mediated p53 signaling pathway.

a. Yanping Zhang, Yue Xiong, Wendell G. Yarbrough. ARF promotes MDM2 degradation and stabilizes p53: ARF-INK4a locus deletion impairs both the Rb and p53 tumor suppression pathways. ***Cell***, 1998, 20;92(6):725-34.

b. Mikael S. Lindström, Aiwen Jin, Chad Deisenroth, and Yanping Zhang. Critical role for Mdm2 central zinc finger in mediating ribosomal protein interaction that is affected by cancer-associated *Mdm2* mutations. ***Mol Cell Biol.*** 2007, 27(3):1056-68.

c. Xuan Meng, Nicole R. Tackmann, Shijie Liu, Jing Yang, Jiahong Dong, Congying Wu, Adrienne D. Cox, and Yanping Zhang. RPL23 links oncogenic RAS signaling to p53-mediated tumor suppression. ***Cancer Research***, 2016 Sep 1;76(17):5030-9..

d. Patrick L. Leslie, Derek A. Franklin, Yong Liu, and Yanping Zhang. p53 Regulates the expression of LRP1 and apoptosis through a stress intensity-dependent microRNA feedback loop. ***Cell Reports***, 2018 7;24(6):1484-1495. doi: 10.1016/j.celrep.2018.07.010.

A Complete List of Published Work in My Bibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/yanping.zhang.1/bibliography/40651128/public/?sort=date&direction=descending