BIOGRAPHICAL SKETCH

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NAME: ZHENG, X.F. STEVEN

eRA COMMONS USERNAME (credential, e.g., agency login): ZHENGXFS

POSITION TITLE: Chief, Division of Cancer Pharmacology

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
Jilin University, Changchun, Jilin	BS	06/1985	Chem & Biochemistry
Harvard Medical School, Boston, MA	PHD	06/1993	Biol Chem & Mol Pharm
Harvard University/HHMI, Cambridge, MA	Postdoctoral Fellow	01/1997	Chemical Biology

A. Personal Statement

My longstanding research interest is to understand mTOR signaling in the biology and therapy of cancer. mTOR pathway is a major oncogenic driver and therapeutic target that is frequently mutated in human cancer. As a postdoctoral fellow with Dr. Stuart Schreiber, I demonstrated that TOR is the direct target of rapamycin and elucidated the mechanism of rapamycin action (**Cell** 82:121; **PNAS** 92:4947). I further showed that rapamycin is a partial TOR inhibitor, and that TOR kinase domain is not inhibited by rapamycin (**Cell** 82:121). The latter finding provided a rationale for developing TOR kinase inhibitors as anticancer agents. My laboratory has contributed to the understanding of nutrient sensing and nuclear mTOR signaling (**Cancer Cell** 26:754; **Mol Cell** 70:502). For example, we discovered a novel, Rab1A-mediated amino acid sensing-signaling mechanism upstream of mTORC1 (**Cancer Cell** 26:754). Rab1A is overexpressed in colorectal cancer, driving cancer cell growth, and rendering sensitivity of cancer cells to mTOR-targeted therapies. mTORC1 is well known as a cytoplasmic kinase that regulates translation and autophagy. We discovered that mTORC1 also serves as a transcription factor that directly binds to promoters and regulates rRNA and tRNA genes (**Nature** 442:1058, **EMBO J.** 28:2220). Moreover, we showed that mTOR controls gene expression through epigenetic and chromatin-dependent mechanisms, which underlies response and resistance to mTOR-targeted agents. Together with studies from several other laboratories, we demonstrated that nuclear mTORC1 signaling controls diverse cell growth and metabolic programs important for normal physiology and diseases, particularly cancer. I have considerable experience in pharmacological targeting of cancer. I have served on many relevant NIH study sections (e.g., BMCT, MCT1, P01 and CCSG Site Visit). My lab has been continuously funded by NIH/NCI for the past 23 years. I have been Co-Leader of the Cancer Pharmacology (CP) Program at the NCI-designated Comprehensive Cancer Center of Rutgers and Princeton Universities since 2012. During this period, CP Program has seen continuous major expansion of cancer-focused and multi-PI funding, and high impact and collaborative publications over the previous two funding cycles. I am confident that under my leadership, CP Program will stay on the upward trajectory, making new ground-breaking discoveries and contributing to better outcomes for cancer patients.

Ongoing and recently completed projects that I would like to highlight include:

NIH/NCI R01 CA260006 Zheng (PI)
07/01/2021 – 06/31/2026
Metabolic Control and Anticancer Mechanism

NIH/NIDDK R01 DK124897 Zheng (PI)
09/18/2020 – 07/31/2024
Amino Acids-Rab1A Nutrient Signaling in the Regulation of Glucose Homeostasis

NIH/NCI P30 CA072720 Libutti (PI)
Role: Program Co-Leader

03/01/1997 - 02/29/2024
NCI-designated Comprehensive Cancer Center Support Grant

NJCSCR-19IRG070 Zheng (PI)
05/01/2019 – 04/30/2023
New Jersey Commission on Spinal Cord Injury Research Role of Maf1 in Neuroprotection and Axonal Regeneration After SCI

NIH/NCI R01 CA173519 Zheng (PI)
08/14/2013 - 05/31/2020
Role of Rab1 in Cell Growth and Cancer

NJCCR-DFHS18CRF007 Zheng (PI)
01/01/2018 - 12/30/2020
NJ Commission on Cancer Research MAF1 in Hepatocellular Carcinoma Pathogenesis and Therapy

NIH/NCI R01 CA123391 Zheng (PI)
04/01/2007 - 02/28/2019
Growth Control and Anti-cancer Mechanisms

Citations:

1. Tsang CK, Chen M, Cheng X, Qi Y, Chen Y, Das I, Li X, Vallat B, Fu LW, Qian CN, Wang HY, White E, Burley SK, **Zheng XFS**. SOD1 Phosphorylation by mTORC1 Couples Nutrient Sensing and Redox Regulation. Mol Cell. 2018 May 3;70(3):502-515.e8. PubMed Central PMCID: PMC6108545.
2. Thomas JD, Zhang YJ, Wei YH, Cho JH, Morris LE, Wang HY, **Zheng XF**. Rab1A is an mTORC1 activator and a colorectal oncogene. Cancer Cell. 2014 Nov 10;26(5):754-69. PubMed Central PMCID: PMC4288827.
3. Li H, Tsang CK, Watkins M, Bertram PG, **Zheng XF**. Nutrient regulates Tor1 nuclear localization and association with rDNA promoter. Nature. 2006 Aug 31;442(7106):1058-61. PubMed PMID: 16900101.
4. **Zheng XF**, Florentino D, Chen J, Crabtree GR, Schreiber SL. TOR kinase domains are required for two distinct functions, only one of which is inhibited by rapamycin. Cell. 1995 Jul 14;82(1):121-30. PubMed PMID: 7606777.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2014 -	Chief, Division of Cancer Pharmacology, Rutgers University - Robert Wood Johnson Medical School, New Brunswick, NJ
2013 -	Full Professor with tenure and University Professor, Department of Pharmacology, Rutgers University - Robert Wood Johnson Medical School, Piscataway, NJ
2013 -	Senior Resident Member, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ
2012 -	Co-Leader, Cancer Pharmacology Program, NCI-designated Comprehensive Cancer Center Consortium of Rutgers University and Princeton University, New Brunswick, NJ
2007 - 2013	Full Professor with tenure and University Professor, Department of Pharmacology, UMDNJ - Robert Wood Johnson Medical School, Piscataway, NJ
2004 - 2013	Member, NCI-designated Comprehensive Cancer Center Consortium of Rutgers University and Princeton University, New Brunswick, NJ
2004 - 2007	Associate Professor with tenure, Department of Pharmacology, UMDNJ - Robert Wood Johnson Medical School, Piscataway, NJ
1999 - 2004	Assistant Professor of Pathology, Department of Pathology, Washington University School of Medicine, St Louis, MO
1997 - 2004	Assistant Professor of Molecular Oncology, Department of Medicine, Washington University School of Medicine, St Louis, MO

Journal Reviewer

Science, Cell, Nature, Molecular Cell, Nature Cell Biology, Nature Chemical Biology, Nature Protocols, Nature Communications, Nature Rev Drug Discovery, Nature Rev Clinical Oncol, Science Signaling, Science Translational Medicine, Hepatology, PLoS Biology, PLoS Genetics, PLoS One, EMBO J, EMBO Rep, Gene & Dev, Mol Biol Cell, Mol Cell Biol, PNAS, Immunity, Drug Discovery Today, Cell Chemical Biology, Cancer Research, Mol Cancer Ther, Oncogene, Endocrine Related Cancer, Carcinogenesis, J Biol Chem, FEMS Yeast Res, Am J Pathol, Genetics

Study Sections and Review Panels

2021 -	Cancer Therapeutics and Drug Development Study Section ZRG1 OTC1-M (80)
2009 - 2022	Department of Defense-CDMRP TSC and NF Review Panels
2019 - 2021	Ad hoc reviewer, NCI Molecular Cancer Therapeutics 1 (MCT1) Study Section
2020	NCI P01 Study Section III
2019 - 2020	Department of Defense-CDMRP Pre-Diabetes Review Panel
2015 - 2020	NCI Clinical and Translational R21/R03 Programs Review Panels
2018	NCI CCSG Site Visit Team Member
2016	NCI R50 Research Specialist Review Panel
2016	Ad hoc Member, NCI Basic Mechanism of Cancer Therapeutics (BMCT) Study Section
2014 - 2016	NCI Omnibus R21/R03 Review Panel
2011 - 2016	National Judge, Siemens Competition in Math, Science and Technology
2014 - 2015	NCI PAR Panel: Transl Res in Pediatric and Obstetric Pharmacology and Therapeutics
2014	NCI Pilot Study: Peer Review Quality of Oncology-2 Study Sections
2014	NCI Cancer Biology-2 Special Emphasis Panel
2010 - 2014	NIH Cell Biology Special Emphasis Panel
2011 - 2013	NIH Cancer Diagnostics and Therapy (CDT) Study Section
2009 - 2011	Charter Member, NIH/NCI Basic Mechanism of Cancer Therapeutics (BMCT) Study Section
2009 - 2010	NIH ZRG1 Cell Biology SEP
2009	NIH ZRG1 OTC-W (95) Oncology SEP
2009	NIH ZRG1 Oncology 1 - Basic and Translational SEP
2008	NIH/NCI ZRG1 ONC-U (92), Cancer Biology and Therapy Pilot Studies
2006 - 2008	Temp. Member, NIH/NCI Basic Mechanism of Cancer Therapeutics (BMCT) Study Section
2006 - 2007	Temp. Member, NIH/NCI Drug Discovery and Molecular Pharmacology (DMP) Study Section
2005	Member, NIH/NCI Centers for Medical Countermeasures against Radiation (CMCR) Review Panel
2004	Member, NIH/NCI National Cooperative Drug Discovery Groups (NCDDG) Review Panel

Editorial Board

Drug Discovery Today (2003-), Translational OncoGenomics (2006-), Trends in Gastroenterology (2015-), Journal of Nutrition and Food Sciences (2015-), Cells (2020-)

Honors

2002 - 2006	Breast Cancer Idea Award, Department of Defense (DOD)
2001 - 2004	Research Award, American Diabetes Association (ADA)
1998 - 2001	HHMI New Faculty Developmental Award, Washington University
1997 - 1998	Coleman Foundation Scholar, Washington University
1994 - 1996	Postdoctoral Fellowship, Damon Runyon Cancer Research Foundation
1992 - 1993	Jeffries Waymen Graduate Scholarship, Harvard University
1986 - 1990	Lucile Markey Biomedical Graduate Fellowship, Harvard University
2004	University Professorship, Rutgers University/UMDNJ
1994	Postdoctoral Fellowship (declined), Leukemia Society of America
1986	Fellowship (Awarded to top 50 biomedical college students from China to pursue PhD study in the USA), CUSBEA

C. Contribution to Science

1. **Nutrient-mTOR Signaling in Normal Physiology and Disease** - mTOR pathway is a master regulator of nutrient signaling. My laboratory elaborated several basic mechanisms by which nutrients regulate mTOR. For examples, we found that Rab1A regulates an ER/Golgi-anchored amino acid signaling to activate mTORC1 independently of Rag GTPases; we showed that mTORC1 dynamically regulates SOD1, a major superoxide dismutase to regulating redox homeostasis in response to nutrient availability. This nutrient-dependent redox mechanism is important for balancing cell growth and survival under normal and starvation conditions.

    a. Zhang X, Wang X, Yuan Z, Radford SJ, Liu C, Libutti SK, **Zheng XFS**. Amino acids-Rab1A-mTORC1 signaling controls whole-body glucose homeostasis. Cell Rep. 2021 Mar 16;34(11):108830. PubMed Central PMCID: PMC8062038.
    b. Tsang CK, Chen M, Cheng X, Qi Y, Chen Y, Das I, Li X, Vallat B, Fu LW, Qian CN, Wang HY, White E, Burley SK, **Zheng XFS**. SOD1 Phosphorylation by mTORC1 Couples Nutrient Sensing and Redox Regulation. Mol Cell. 2018 May 3;70(3):502-515.e8. PubMed Central PMCID: PMC6108545.
    c. Thomas JD, Zhang YJ, Wei YH, Cho JH, Morris LE, Wang HY, **Zheng XF**. Rab1A is an mTORC1 activator and a colorectal oncogene. Cancer Cell. 2014 Nov 10;26(5):754-69. PubMed Central PMCID: PMC4288827.
    d. Li H, Tsang CK, Watkins M, Bertram PG, **Zheng XF**. Nutrient regulates Tor1 nuclear localization and association with rDNA promoter. Nature. 2006 Aug 31;442(7106):1058-61. PubMed PMID: 16900101.

2. **Nuclear mTOR Signaling and Transcriptional Regulation** - mTOR is known as a cytoplasmic kinase that regulates translation and autophagy. However, we discovered that mTOR is localized in the nucleus and binds to promoters and regulate transcription of growth and metabolic genes important for important for normal physiology and diseases, particularly cancer. Moreover, we showed that mTOR controls gene expression through epigenetic and chromatin-dependent mechanisms.

    a. Ren QN, Zhang H, Sun CY, Zhou YF, Yang XF, Long JW, Li XX, Mai SJ, Zhang MY, Zhang HZ, Mai HQ, Chen MS, **Zheng XFS**, Wang HY. Phosphorylation of androgen receptor by mTORC1 promotes liver steatosis and tumorigenesis. Hepatology. 2022 May;75(5):1123-1138. PubMed Central PMCID: PMC9300126.
    b. Zhang S, Zhou YF, Cao J, Burley SK, Wang HY, **Zheng XFS**. mTORC1 Promotes ARID1A Degradation and Oncogenic Chromatin Remodeling in Hepatocellular Carcinoma. Cancer Res. 2021 Nov 15;81(22):5652-5665. PubMed Central PMCID: PMC8595749.
    c. Wei Y, Tsang CK, **Zheng XF**. Mechanisms of regulation of RNA polymerase III-dependent transcription by TORC1. EMBO J. 2009 Aug 5;28(15):2220-30. PubMed Central PMCID: PMC2726700.
    d. Li H, Tsang CK, Watkins M, Bertram PG, **Zheng XF**. Nutrient regulates Tor1 nuclear localization and association with rDNA promoter. Nature. 2006 Aug 31;442(7106):1058-61. PubMed PMID: 16900101.

3. **Nutrient Signaling and Stress Responses** - Nutrient signaling plays an important role in dynamic control of cellular stress responses, which is important to maintain rapid growth in the presence of nutrients and sustain survival under starvation. For example, our recent study revealed a conserved mechanism by which eukaryotic cells, including yeast and cancer cells, couple nutrient signaling to dynamically regulate redox homeostasis through mTOR-dependent phosphorylation of superoxide dismutase 1 (SOD1).

    a. Wang X, Zhang H, Sapio R, Yang J, Wong J, Zhang X, Guo JY, Pine S, Van Remmen H, Li H, White E, Liu C, Kiledjian M, Pestov DG, Steven **Zheng XF**. SOD1 regulates ribosome biogenesis in KRAS mutant non-small cell lung cancer. Nat Commun. 2021 Apr 15;12(1):2259. PubMed Central PMCID: PMC8050259.
    b. Tsang CK, Chen M, Cheng X, Qi Y, Chen Y, Das I, Li X, Vallat B, Fu LW, Qian CN, Wang HY, White E, Burley SK, **Zheng XFS**. SOD1 Phosphorylation by mTORC1 Couples Nutrient Sensing and Redox Regulation. Mol Cell. 2018 May 3;70(3):502-515.e8. PubMed Central PMCID: PMC6108545.
    c. Tsang CK, Liu Y, Thomas J, Zhang Y, **Zheng XF**. Superoxide dismutase 1 acts as a nuclear transcription factor to regulate oxidative stress resistance. Nat Commun. 2014 Mar 19;5:3446. PubMed Central PMCID: PMC4678626.

d. Ai W, Bertram PG, Tsang CK, Chan TF, **Zheng XF**. Regulation of subtelomeric silencing during stress response. Mol Cell. 2002 Dec;10(6):1295-305. PubMed PMID: 12504006.

4. **Therapeutic Targeting of mTOR** - I have contributed to understanding mechanisms of therapeutic targeting of mTOR. I showed that FKBP12-rapamycin complex directly binds to mTOR through the FRB (FKBP-rapamycin-binding) domain and that rapamycin is only a partial inhibitor of mTOR (Cell 82: 121; PNAS 92: 4947). The latter finding which provided a key rationale for developing TOR kinase inhibitors as anticancer agents. My lab performed the first genomic profiling of rapamycin sensitivity and resistance genes (PNAS 97: 13227). My lab showed a mechanism by which a non-gatekeeper mutation in the ATP-binding site of mTOR renders acquired resistance to mTOR kinase inhibitors in cancer (Cell Rep 11:446).

   a. Wu TJ, Wang X, Zhang Y, Meng L, Kerrigan JE, Burley SK, **Zheng XF**. Identification of a Non-Gatekeeper Hot Spot for Drug-Resistant Mutations in mTOR Kinase. Cell Rep. 2015 Apr 21;11(3):446-59. PubMed Central PMCID: PMC4761412.
   b. Chan TF, Carvalho J, Riles L, **Zheng XF**. A chemical genomics approach toward understanding the global functions of the target of rapamycin protein (TOR). Proc Natl Acad Sci U S A. 2000 Nov 21;97(24):13227-32. PubMed Central PMCID: PMC27207.
   c. **Zheng XF**, Florentino D, Chen J, Crabtree GR, Schreiber SL. TOR kinase domains are required for two distinct functions, only one of which is inhibited by rapamycin. Cell. 1995 Jul 14;82(1):121-30. PubMed PMID: 7606777.
   d. Chen J, **Zheng XF**, Brown EJ, Schreiber SL. Identification of an 11-kDa FKBP12-rapamycin-binding domain within the 289-kDa FKBP12-rapamycin-associated protein and characterization of a critical serine residue. Proc Natl Acad Sci U S A. 1995 May 23;92(11):4947-51. PubMed Central PMCID: PMC41824.

5. **mTOR Signaling in Liver Pathogenesis and Therapies** - mTOR pathway is commonly activated and is a major driver in liver cancer. My lab has elucidated several mechanisms by which mTOR pathway is activated and how mTOR pathway activation promotes hepatocarcinogenesis. For example, our recent work revealed that upon oncogenic activation, mTOR promotes oncogenic chromatin remodeling through proteasome-dependent degradation of the tumor suppressor ARID1A in hepatocellular carcinoma (Cancer Res 2021). We also showed that mTOR and androgen receptor pathways cross-talk with each other in promoting male-dominant liver cancer development and therapeutic resistance to US FDA-approved oncology drugs everolimus and enzalutamide (Hepatology 2018; Hepatology 2021).

   a. Ren QN, Zhang H, Sun CY, Zhou YF, Yang XF, Long JW, Li XX, Mai SJ, Zhang MY, Zhang HZ, Mai HQ, Chen MS, **Zheng XFS**, Wang HY. Phosphorylation of androgen receptor by mTORC1 promotes liver steatosis and tumorigenesis. Hepatology. 2022 May;75(5):1123-1138. PubMed Central PMCID: PMC9300126.
   b. Zhang S, Zhou YF, Cao J, Burley SK, Wang HY, **Zheng XFS**. mTORC1 Promotes ARID1A Degradation and Oncogenic Chromatin Remodeling in Hepatocellular Carcinoma. Cancer Res. 2021 Nov 15;81(22):5652-5665. PubMed Central PMCID: PMC8595749.
   c. Zhang H, Li XX, Yang Y, Zhang Y, Wang HY, **Zheng XFS**. Significance and mechanism of androgen receptor overexpression and androgen receptor/mechanistic target of rapamycin cross-talk in hepatocellular carcinoma. Hepatology. 2018 Jun;67(6):2271-2286. PubMed Central PMCID: PMC6106789.
   d. Li Y, Tsang CK, Wang S, Li XX, Yang Y, Fu L, Huang W, Li M, Wang HY, **Zheng XF**. MAF1 suppresses AKT-mTOR signaling and liver cancer through activation of PTEN transcription. Hepatology. 2016 Jun;63(6):1928-42. PubMed Central PMCID: PMC5021206.

Complete List of Published Work in My Bibliography:
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