## BIOGRAPHICAL SKETCH

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NAME: Shen, Zhiyuan

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

POSITION TITLE: Professor of Radiation Oncology, Professor of Pharmacology,
Chief of Division of Radiation 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 |
|---|---|---|---|
| Norman Bethune University of Medical Sciences (Jilin University School of Medicine), Jilin, China | MD | 08/1985 | Medicine |
| Beijing Institute of Radiation Medicine, China | MS | 08/1988 | Radiation Medicine & toxicology |
| Department of Radiological Health Sciences, Colorado State University, Fort Collins, CO, USA | PhD | 05/1993 | Cell & Molecular Radiobiology |
| Colorado State University, Fort Collins, CO, USA | Postdoctoral | 02/1994 | Cell & Molecular Biology (cytochrome p450) |
| Los Alamos National Laboratory, Los Alamos, New Mexico, USA | Postdoctoral | 09/1996 | Cell & Molecular Biology (DNA repair) |

### A. Personal Statement

I am an experienced cancer biologist with strong expertise in radiation biology, DNA damage response, and animal models of tumorigenesis. My research interests are to understand the mechanisms by which genomic instability is provoked and contributes to tumorigenesis, and to exploit the therapeutic vulnerability of cancers with defective response to DNA damage. Since 1997, I have served as the PI for 6 NIH R01 projects, 4 DOD breast cancer research projects, and a P01 project. My lab is proficient in many technical aspects including molecular biology, animal models, radiation biology, and translational research. I have successfully trained several graduate students and postdoctoral fellows, and I am experienced with guiding lab personnel to design and conduct efficient and scientifically sound experiments. I have proven skills in academic and administrative leadership. I am the Inaugural Chief of a productive Division of Radiation Cancer Biology in the Department of Radiation Oncology. I was a Program Co-Leader of the Genomic Instability and Cancer Genetics Program of the Rutgers Cancer Institute of New Jersey (CINJ) between 2008 and 2022 and was recently appointed Associate Director for Basic Research at CINJ. I am confident that I will effectively lead the success of the CCSG basic science programs. Below are a few sample publications in the broad areas of cancer biology, radiation biology, and development biology.

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

2R01CA195612-06A1
Shen (PI)
07/01/2021 – 06/30/2026
Molecular modulators of radiation-induced chromosome instability and hematopoietic damage

1P01CA250957-01A1
Shen (PI)
05/01/2021 – 04/30/2026
Mechanisms of the BRCA-network in tumorigenesis and therapeutic response

1R01CA260724-01
Shen (PI)
02/01/2021-01/31/2026
Regulation of KU70 methylation and functions by SETD4

5P30CA072720-22
Libutti (PI), Role: Co-leader, Genomic Instability and Cancer Genetics Program
03/01/2019-02/29/2024
Cancer Center Support Grant (CCSG)

Citations:


1. Wang Y, Liu B, Lu H, Liu J, Romanienko PJ, Montelione GT, **Shen Z*.** SETD4-mediated KU70 methylation suppresses apoptosis. Cell Rep. 2022;39(6):110794. Epub 2022/05/12. doi: 10.1016/j.celrep.2022.110794. PubMed PMID: 35545041.
2. Ye C, Liu B, Lu H, Liu J, Rabson AB, Jacinto E, Pestov DG, **Shen Z***. BCCIP is required for nucleolar recruitment of eIF6 and 12S pre-rRNA production during 60S ribosome biogenesis. Nucleic Acids Res. 2020 Dec 16;48(22):12817-12832. doi: 10.1093/nar/gkaa1114. PubMed PMID: 33245766.
3. Choi WS, Liu B, **Shen Z***, Yang W*. Structure of human BCCIP and implications for binding and modification of partner proteins. Protein Sci. 2021 Mar;30(3):693-699. doi: 10.1002/pro.4026. Epub 2021 Jan 29. PubMed PMID: 33452718.
4. Lu H, Ye C, Liu J, Rabson AB, Verzi M, De S, **Shen Z***. Requirement of Bccip for the Regeneration of Intestinal Progenitors. Am J Pathol. 2021 Jan;191(1):66-78. doi: 10.1016/j.ajpath.2020.09.009. Epub 2020 Oct 9. PubMed PMID: 33039352.


**B. Positions, Scientific Appointments, and Honors**

| | |
|---|---|
| 2022 – present | Associate Director for Basic Science, Rutgers Cancer Institute of New Jersey |
| 2008 – Present | Professor (tenured) of Radiation Oncology, Pharmacology, Department of Radiation Oncology, the Rutgers Cancer Institute of New Jersey and Rutgers Robert Wood Johnson Medical School, Rutgers, The State University of New Jersey, New Brunswick, NJ |
| 2008 – 10/2022 | Co-leader, Genomic Instability and Cancer Genomics program (12/2008-Present), NCI Designated Comprehensive Cancer Center at Rutgers Cancer Institute of New Jersey. |
| 2006 – Present | Chief of Division of Radiation Cancer Biology, Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, Robert Wood Johnson Medical School (legacy University of Medicine and Dentistry of New Jersey), Rutgers, The State University of New Jersey. |
| 2006 – 2011 | University Professorship Award, University of Medicine and Dentistry of New Jersey (UMDNJ), New Jersey, USA |
| 2006 – 2008 | Associate Professor (tenured) of Radiation Oncology, Pharmacology, Department of Radiation Oncology, Cancer Institute of New Jersey, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey. |
| 2003 – 2006 | Associate Professor (tenured), Department of Molecular Genetics and Microbiology, University of New Mexico School of Medicine, Albuquerque, NM |
| 2002 – 2006 | Career Development Award (CDA), Breast Cancer Research Program, US Department of Defense |
| 2000 – 2003 | Assistant Professor (tenure-track), Department of Molecular Genetics and Microbiology, University of New Mexico School of Medicine, Albuquerque, NM |
| 1997 – 2000 | Assistant Professor (tenure-track), Cancer Center and Department of Molecular Genetics, University of Illinois at Chicago, Chicago, IL. |
| 1996 – 2001 | First Independent Research Support & Transition (FIRST) Awards (R29), NIH |
| 1996 – 1997 | Research and Development Award, Los Alamos National Laboratory |

1994 – 1997 Director's Postdoctoral Fellow with Dr. David J Chen (02/1994-09/1996), and Staff Member (09/1996-05/1997), Life Sciences Division, Los Alamos National Lab, Los Alamos, New Mexico.
1994 – 1996 Director's Postdoctoral Fellowship Award, Los Alamos National Laboratory
1990 – 1994 Graduate Research Assistant (01/1990-05/1993) and Postdoctoral Fellow (05/1993-02/1994) with Dr. Mortimer M. Elkind, Dept. of Radiological Health Sciences, Colorado State University, Fort Collins, Colorado.

**C. Contributions to Science**

1. **Cytochrome *p450-1b1* and chemical carcignogenesis** (in the early 1990's, PhD student). Based on a careful metabolite profile analysis of the available publications and some of my own data with C3H101/2 cells, I concluded that there must be a new isoform of cytochrome p450 responsible for metabolizing polycyclic aryl hydrocarbons in these cells (a). I designed a novel molecular approach, and successfully identified this new cytochrome p450 that was initially called p450CMEF (a). I then, for the first time, cloned and sequenced the full-length cDNA of the same gene that was later designated as Cytochrome p450-1b1 (b). I further characterized the role of this gene in chemical carcinogenesis *in vitro* (c). My works had set up a stage for a large field of scientific works in chemical and hormone induced carcinogenesis in relation to p450.

    a. **Shen Z**, Wells RL, Liu J, and Elkind MM. (1993) Identification of a cytochrome P450 gene by reverse transcription--PCR using degenerate primers containing inosine. *Proceedings of the National Academy of Sciences of the United States of America*, **90**, 11483-11487.
    b. **Shen Z**, Liu J, Wells RL, and Elkind MM. (1994) cDNA cloning, sequence analysis, and induction by aryl hydrocarbons of a murine cytochrome P450 gene, Cyp1b1. *DNA and cell biology*, **13**, 763-769.
    c. **Shen Z**, Wells RL, and Elkind MM. (1994) Enhanced cytochrome P450 (Cyp1b1) expression, aryl hydrocarbon hydroxylase activity, cytotoxicity, and transformation of C3H 10T1/2 cells by dimethylbenz(a)anthracene in conditioned medium. *Cancer research*, **54**, 4052-4056.

2. **Mammalian RAD52 and homologous recombination.** Prior to early 1990's, there was little studies on the mammalian homologous recombination (HR) due to the lack of information on a key mammalian homologue of HR protein Rad52, despite of the identification of the yeast counterpart in 1983. I pioneered the study on mammalian HR by firstly cloning the human and mouse RAD52 cDNA (a). As a none-tenure track junior PI, I documented the interactions between human RAD52 and RAD51 (b) and reported the RAD52 self-association and domains required for this association (c), which forms the bases of RAD52 oligomerization. After becoming a tenure-track PI, I continued to work on RAD52 and reported that human RAD52 interact with RNA Polymerase II complex and proposed that this interaction may suggest "a functional role of RAD52 in targeting DNA damage on transcription active loci to recombinational repair" (d). This concept was somewhat under-appreciated at that time, but there is a renewed interest in transcription-enhanced HR and the potential role of RAD52 in this process in the recent years.

    a. **Shen Z**, Denison K, Lobb R, Gatewood JM, and Chen DJ. (1995) The human and mouse homologs of the yeast RAD52 gene: cDNA cloning, sequence analysis, assignment to human chromosome 12p12.2-p13, and mRNA expression in mouse tissues. *Genomics*, **25**, 199-206.
    b. **Shen Z**, Cloud KG, Chen DJ, and Park MS. (1996) Specific interactions between the human RAD51 and RAD52 proteins. *The Journal of biological chemistry*, **271**, 148-152.
    c. **Shen Z**, Peterson SR, Comeaux JC, Zastrow D, Moyzis RK, Bradbury EM and Chen DJ. (1996) Self-association of human RAD52 protein. *Mutation research*, **364**, 81-89.
    d. Liu J, Meng X, and **Shen Z**. (2002) Association of human RAD52 protein with transcription factors. *Biochemical and biophysical research communications*, **297**, 1191-1196.

3. **Identifications of two key players in the sumoylation pathway: UBL1 (SUMO-1) and UBE2I (UBC9**). In 1996, I was fortunately to be one of the original investigators who reported two of the key components of the sumoylation pathway (a & b), which I named as UBL1 for Ubiquitin-Like protein 1 and UBE2I for ubiquitin-conjugating enzyme E2I (now commonly known as SUMO-1 and UBC9). After I became a tenure-track PI in 1997, I continued to work on the function of this pathway in DNA repair (c) and collaborated with others to

understand the roles of sumoylation in p53, Tel, and Topoisomerase functions, while creating new research identity that is distinct from my postdoctoral work. I co-published several papers with at least 5 different research groups on these topics (see complete publication list). Perhaps a significant contribution of these collaborations is the elucidation of why UBC9 is a specific E2 conjugation enzyme for SUMO-1/UBL1, but not for the structurally similar ubiquitin (d). These works undoubtly have contributed to the elucidation of one of the most important post-translational protein modification pathways in modern biology.

a. **Shen Z**, Pardington-Purtymun PE, Comeaux JC, Moyzis RK, nd Chen DJ. (1996) UBL1, a human ubiquitin-like protein associating with human RAD51/RAD52 proteins. *Genomics*, **36**, 271-279.
b. **Shen Z**, Pardington-Purtymun PE, Comeaux JC, Moyzis RK, and Chen DJ. (1996) Associations of UBE2I with RAD52, UBL1, p53, and RAD51 proteins in a yeast two-hybrid system. *Genomics*, **37**, 183-186.
c. Li W, Hesabi B, Babbo A, Pacione C, Liu J, Chen DJ, Nickoloff JA, and **Shen Z**. (2000) Regulation of double-strand break-induced mammalian homologous recombination by UBL1, a RAD51-interacting protein. *Nucleic acids research*, **28**, 1145-1153.
d. Liu Q, Jin C, Liao X, **Shen Z**, Chen DJ and Chen Y. (1999) The binding interface between an E2 (UBC9) and a ubiquitin homologue (UBL1). *The Journal of biological chemistry*, **274**, 16979-16987.

4. **Novel mechanisms for maintenance of genomic stability by BCCIP gene, and the SIRP mode of tumor suppressors.** In the late 1990's, a significant advance in cancer biology is the realization that the BRCA1 and BRCA2 proteins are part of the homologous recombination pathways. However, it was quite puzzling that while BRCA1/2 germline carriers are highly penetrative to cancer, BRCA mutations are quite rare in the sporadic cancers. I realized that this perhaps indicates that the defects of additional genes in the same pathway of BRCA contribute to the rest of cancers. Once becoming a PI in 1997, I immediately initiated an effort to identify additional genes in the same pathway of BRCA2, and this led me to identify the novel BCCIP gene that has fascinated my scientific career in the last >20 years. We have identified its role in DNA homologous recombinational repair of DNA double strand breaks (various publications in 2005-2007) and cell cycle progression (various publications in 2004-2009) and found that it also has a critical role in chromosome stability and mitotic chromosome segregation (a). We also found that BCCIP is down-regulated in several tumor types, and the down-regulation of BCCIP dictate the therapeutic outcomes including radiation therapy. However, perhaps an even more significant aspect of these studies is the concept development of the SIRP (Suppressor of Initiation but Required for Progression) (b). On one hand, a subtle defect of BCCIP was sufficient to trigger genomic instability so that BCCIP fits a prototype of caretaker tumor suppressor. On the other hand, BCCIP is an essential gene indispensable for cell proliferation thus needed for tumor progression, and cancer cells may not be able to tolerate complete loss of BCCIP. How to reconcile these apparently opposing aspects that are unique to many essential caretaker genes? My lab developed a reversible conditional shRNA based transgenic mouse model (b) and demonstrated that only a transient and partial down-regulation of BCCIP is sufficient to trigger tumorigenesis and the down-regulated BCCIP status must be reversed spontaneously to allow tumor progression. This leads to the concept of SIRP (Suppressor of Initiation but Required for Progression) that may modulate tumorigenesis via transient, non-mutagenic mechanisms, and sometimes opposing effect at different stages of tumorigenesis. We continue to develop various mouse models to elucidate Bccip's role in tumorigenesis (c, d).

a. Meng X, Fan J, and Shen Z. (2007) Roles of BCCIP in chromosome stability and cytokinesis. Oncogene, 26, 6253-6260.
b. Huang YY, Dai L, Gaines D, Droz-Rosario R, Lu H, Liu J. and Shen Z. (2013) BCCIP Suppresses Tumor Initiation but Is Required for Tumor Progression. Cancer research, 73, 7122-7133.
c. Droz-Rosario R, Lu H, Liu J, Liu NA, Ganesan S, Xia B, Haffty BG, Shen Z. (2017) Roles of BCCIP deficiency in mammary tumorigenesis. Breast cancer research: BCR 2017;19:115
d. Huhn SC, Liu J, Ye C, Lu H, Jiang X, Feng X, Ganesan S, White E, and Shen Z. (2017) Regulation of spindle integrity and mitotic fidelity by BCCIP. Oncogene 36:4750-66

5. **Others:** role of cytoskeleton protein Filamin-A in DNA damage response, cancer biomarkers, and radiation sensitivity syndrome. My lab has also been interested in identifying cancer biomarkers and target for therapy. We identify Filamin-A has a novel function in DNA damage response thus can be used as a marker and target to modulate cancer metastasis and sensitization to therapeutic DNA damage (a-c). We are also

responsible to demonstrate that DNA ligaseIV mutation account for a subtype of Dubowitz syndrome patients (d).


a. Yuan Y, and **Shen Z**. (2001) Interaction with BRCA2 suggests a role for filamin-1 (hsFLNa) in DNA damage response. *The Journal of biological chemistry*, **276**, 48318-48324.
b. Meng X, Yuan Y, Maestas A, and **Shen Z**. (2004) Recovery from DNA damage-induced G2 arrest requires actin-binding protein filamin-A/actin-binding protein 280. *The Journal of biological chemistry*, **279**, 6098-6105.
c. Yue J, Wang Q, Lu H, Brenneman M, Fan F, and **Shen Z.** (2009) The cytoskeleton protein filamin-A is required for an efficient recombinational DNA double strand break repair. *Cancer research*, **69**, 7978-7985.
d. Yue J, Lu H, Lan S, Liu J. Stein MN, Haffty BG, and **Shen Z**. (2013) Identification of the DNA repair defects in a case of Dubowitz syndrome. PLoS One 8:e54389.


**Complete List of Published Work in MyBibliography** can be found at:
http://www.ncbi.nlm.nih.gov/sites/myncbi/zhiyuan.shen.1/bibliography/45207792/public/?sort=date&direction=descending.