BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Yuhui Whitney Yin

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

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)*	Completion Date MM/YYYY	FIELD OF STUDY
Tianjin Medical College, Tianjin, China	MD	1989	Medicine
University of North Carolina at Chapel Hill, NC	PhD	1996	Biochemistry / Biophysics
Yale University	Postdoc	1998-2002	Biophysics

A. Personal Statement

My research focuses on human mitochondrial DNA (mtDNA) replication and repair as well as RNA transcription with emphases on illustrating mechanism of antiviral mitochondrial toxicity and mitochondrial dysfunction implicated human diseases. Our long-term goal is to provide structural and functional insight on the implication erroneous mtDNA replication in human diseases, and to understand and eventually to overcome antiviral drug toxicity.

Our approach is combined methods of structural biology, enzyme kinetics and synthetic chemistry. My laboratory determined the first crystal structure of human DNA replicase – mitochondrial DNA polymerase holoenzyme (Polγ). This progress significantly advanced the field, as it provided a framework for further studies of mutations in mitochondrial DNA polymerase implicated in human diseases. We also determined several crystal structures of replicating human Pol γ ternary complexes containing either a substrate nucleotide triphosphate or an antiviral reagent. These structures provide a wealth of structural and functional information in understanding Pol γ mediated drug toxicity. Our research philosophy is to use a set of complementary methods to study a system, as each individual technique has advantage as well as pitfalls. Therefore, our structural work is always accompanied by various functional studies to provide comprehensive viewpoints.

We put significant effort on understand oxidative DNA damage in mitochondria and lesion repairs. We characterized Pol γ function in base excision repair, conducted structural and functional studies on a mitochondrial endo/exonuclease, EXOG, in base excision repair. Importantly, we and others discovered that poly(ADP-ribose) polymerase 1, PARP1 in mitochondria and PARP1 can selectively PARylate Pol γ. We have been carrying out structural and functional studies of effects of UV radiation and oxidative damage on mitochondrial genome maintenance and integrity.

I am well prepared to direct the proposed research. I have completed several sponsored research projects by NIH and Welch Foundation. I have long interest in understanding protein-nucleic acid interaction, specifically enzymes involved in DNA replication, DNA repair and RNA transcription. As postdoc fellow with Dr. Thomas Steitz and graduate student with Dr. Charles Carter, I am well trained in X-ray crystallography and solution structural studies using small angel X-ray scattering system. My laboratory has added cryo-electron microscopy as a major tool for structural biology and have determined several cryo-EM structures relevant to the proposed study. Through collaboration with Drs. Smita Patel and Karen Anderson, I have acquired solid knowledge on enzyme kinetics.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2015-present	Associate professor, University of Texas Medical Branch, Dept of Biochemistry and Molecular biology
2012-2015	Assistant professor, University of Texas Medical Branch, Department of Pharmacology and toxicology
2003 -2011	Assistant professor, University of Texas at Austin, Department of Chemistry and Biochemistry
2001-2003	Associate research scientist, Yale University, Department of Molecular Biophysics and Biochemistry

Other Experience and Professional Memberships

2021	NIH NIEHS, K99/R00 study section
2020	NIH NIEHS, K99/R00 study section
2019	NIH MSFB study section
2010	NIH, NIEHS Ad hoc member of study section
2019-present	Member of Biophysics Society
2003-present	Member of AAAS
2003-present	Member of American Chemical Society
1996-present	Member of American Crystallography Association

Honors

2017-2019	Fulbright fellow, US Department of State, Bureau of Education and Culture Affairs
2014-2016	McLaughlin Award, McLaughlin foundation

C. Contributions to Science

1. Mitochondrial DNA repair

Mitochondria contain high concentrations of reactive oxygen species (ROS) due to intrinsic radicals generated through metabolic reactions and extrinsic factors such as anticancer radiation therapy. Consequently, mitochondrial DNA suffers higher likelihood for oxidative damages than chromosomal DNA. While the overall scheme follows that of nuclear BER, mitochondrial BER has distinct differences. Pol γ is responsible for DNA synthesis during replication and repair. I lead investigation of Pol γ activity in BER specific gap-filling DNA synthesis. Our findings indicate Pol γ is very inefficient on 1-nt gapped DNA and no strand displacement synthesis activity, suggesting that the polymerase alone is inefficient to carry out mitochondrial BER function, supporting the importance of repair complex. We studied Pol γ replication on damaged DNA. We recent started structural and functional studies of components of mitochondrial DNA repair complex with a long-term goal of structural determination of the entire mitochondrial DNA repairsome. I am the PI of these studies.

a. Szymanski, MR., Yu, W., Gmyrek, AM., White, MA., Molineux, IJ., Lee, JC., **Yin, YW**., “A Novel Domain in Human EXOG Converts Apoptotic Endonuclease to DNA Repair Exonuclease”, 2017, **Nature Communications**, 8:14959
b. Wen, JJ, **Yin, YW**, Garg, NJ, “Mitochondrial PARP1 Attenuates POLG-dependent mtDNA Integrity and Contributes to Mitochondrial Dysfunction: Benefits of PARP1 inhibition in Chagasic Cardiomyopathy”, 2018, **PloS Pathog**, 2018 May 31;14(5):e1007065. doi: 10.1371.
c. Anderson, APP, Luo, XM, Russell W, **Yin, YW**., “Oxidative damage diminishes human mitochondrial DNA polymerase fidelity’, 2020, **Nucleic Acids Res**. 24:48(2):817-829.
d. Herrmann GK, Russell WK, Garg NJ, **Yin YW.** Poly(ADP-ribose) Polymerase 1 Regulates Mitochondrial DNA Repair in a Metabolism-Dependent Manner, 2021, **J. Biol Chem**. 296;100300.

2. Structural mechanism of RNA transcription

Despite their difference in structure and sequence, all RNA polymerases catalyzed RNA synthesis present biphasic characteristics: the initiation phase where repetitive short abortive RNAs are synthesized and released, and the elongation phase where long RNAs are synthesized processively. To reveal the structural mechanism for the phase transition, I determined the first RNA polymerase elongation complex to high resolution. I used a synthetic DNA/RNA transcription bubble that tricks the polymerase directly enters elongation phase by bypassing the initiation phase. It was the only RNA polymerase elongation complex that is still active in crystal. This feature enabled me to solve more elongation structures captured at various stages of reaction pathway using *in crystallo* catalysis. Our publications set the stage for many studies of RNA transcription and provided structural basis for the phase transition in transcription reactions. I was the primary investigator in all studies.

a. **Yin, YW**. & Steitz, TA., “Structural Basis for the Transition from Initiation to Elongation Transcription in T7 RNA Polymerase”. 2002, **Science**, 298(5597):1387-95
b. **Yin, YW.** & Steitz, TA., "Mechanism for T7 RNA Polymerase Translocation and Helicase activity". 2004, **Cell**, 116(3):393-404.
c. Ramachandran A, Nandakumar D, Deshpande A, Lucas TP, Bhojappa RR, Tang GQ, Raney K, **Yin YW**, Patel SS. “The Yeast Mitochondrial RNA Polymerase and Transcription Factor Complex Catalyzes Efficient Priming of DNA Synthesis on Single-stranded DNA”, 2016, **J.Biol Chem**, 291(32):16828-39
d. Jain, N, Blauch, LR, Szymanski, MR, Das R, Tang, SKY, **Yin, YW** and Fire, AZ, “Transcription Polymerase-catalyzed Emergence of Novel RNA Replicons”, 2020, **Science**, 368(153): 1-11

3. Structural and functional studies of antiviral drug toxicity

Antiviral drugs based on nucleoside analogs are effective inhibitors for viral reverse transcriptase and RNA polymerase, thus have been successfully used in treating HIV and HCV infections. With prolonged patients life span, the success of the drugs now has to be balanced with their drug toxicity. One of the major target of nucleoside analogs is human mitochondrial DNA polymerase, Pol γ. Because drug efficacy is not completely correlated with drug toxicity, we believe there is exploitable difference in designing potent, low toxic antiviral reagents. To reveal the structural differences between viral target protein and human adverse reaction target, we embarked on structural and functional studies of replicating human mitochondrial DNA polymerase or stalled by antiviral drugs. My laboratory determined the first crystal structures of human Pol γ holoenzyme. Recently, we determined structures of ternary complex of Pol γ -DNA with a substrate or an anti-HIV reagent, zalcitabine, lamivudine or emtricitabine. These structures provided unprecedented insight in Pol γ mediated antiviral drug toxicity. As Pol γ mutations are associated with multisystem disorders, the structures have been widely used by basic scientists as well as clinicians to understand the detrimental effects of the mutations. I directed all of these studies.

a. Lee, YS, Kennedy, WD, **Yin, YW**, “Structural Insights into Human Mitochondrial DNA Replication and Disease-related Polymerase Mutations”, 2009, **Cell**, 139(2):312-324. [commentary in **Cell,** 2009,139(2):231-233]
b. Sohl, CS., Szymanski, MR., Mislak, AC., Shumate, CK., Amiralaei, S., Schinazi, RF., Anderson, KS., **Yin, YW.,** “Probing the Structural and Molecular Basis of Nucleotide Selectivity by Human Mitochondrial DNA Polymerase γ, 2015, **PNAS**, 112(28):8596-601.
c. Szymanski, MR., Kuznestov, VB., Shumate, CK., Meng, Q., Lee, YS., Patel, G., Patel, S., **Yin, YW.**, “Structural Basis for Processivity and Antiviral Drug Toxicity in Human Mitochondrial DNA Replicase”, 2015, **EMBO J**, 34(14):1959-70.
d. Sowers, ML, Anderson, APP, Wrabl, JO, **Yin, YW**. Networked Communication between Polymerase and Exonuclease Active Sites in Human Mitochondrial DNA Polymerase. 2019, **J Am Chem Soc**., 141(27):10821-10829.

4. Studies of tryptophanyl tRNA synthetase fidelity

To ensure accurate protein synthesis, an aminoacyl tRNA synthetase needs to selectively charge the cognate amino acid and tRNA with precision. My graduate work focused on understanding how *B. stearotheomophilus* tryptophanyl tRNA synthetase (TrpRS), the project aims to understand hwo TrpRS distinguishes the substrate from other amino acids, and from antibiotics that are substrate analogs. I determined crystal structures of TrpRS complexed with either substrate tryptonphan, or analogs tryptophamide, and antibiotic indolmycin. I performed crystallization optimization using statistical method, incomplete factorial design and response surfaces methods. My training laid a solid foundation for crystallography techniques and scientific problem solve skills. I was either primary investigator or collaborator in these studies.

a. Carter, CW. Jr., and **Yin, Y.**, "Quantitative Analysis in the Characterization and Optimization of Protein

Crystal Growth." 1994, **Acta. Cryst.** D50, 572-590

b. **Yin, Y.,** and Carter, CW. Jr., "Incomplete Factorial Design and Response Surfaces Methods: Yield Optimization of tRNA-Trp from in vitro T7 RNA Polymerase Transcription." 1996, **Nucleic Acids Res**, 24, 1279-1286.

c. Rataileau, P., Huang, X., **Yin, YW.**, Vachette, P., Vonrhein, C., Bricogne, G., Roversi, P, Ilyin, V., Carter, CW. Jr., "2.2 A Crystal Structure of Tryptophanyl-tRNA Synthetase Complexed with ATP in a Closed, Pretransition-state Conformation", 2003, **J Mol Biol**, 325(1): 39-63.

d. Williams, TL, **Yin, YW.,** Carter CW Jr., "Selective Inhibition of Bacterial Tryptophanyl-tRNA Synthetases by Indolmycin is Mechanism-Based", **J Biol Chem**. 2016 Jan 1;291(1):255-65.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/yuhui.yin.1/bibliography/48322525/public/?sort=date&direction=ascending