BIOGRAPHICAL SKETCH

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NAME: Yuhui Whitney Yin

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

POSITION TITLE: 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	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 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 mitochondrial DNA 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 (Pol γ). 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 □□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 □. We further conducted biochemical studies to examine the effect of PARP1-Pol □□interaction on mtDNA replication and repair.

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 and Honors

Postitions and Employment

1998-2001 Postdoctoral fellow, Yale University. Advisor: Thomas A Steitz.
2001-2003 Associate research scientist, Yale University, Department of Molecular Biophysics and Biochemistry

2003 -2011- Assistant professor, University of Texas at Austin, Department of Chemistry and Biochemistry
2012-2015 Assistant professor, University of Texas Medical Branch, Department of Pharmacology and toxicology
2015-present Associate professor, University of Texas Medical Branch, Department of Pharmacology and toxicology

Other Experience and Professional Memberships

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

Honors

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

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 □□is responsible for DNA synthesis during replication and repair. I lead investigation of Pol □□activity in BER specific gap-filling DNA synthesis. Our findings indicate Pol □□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 □□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(6487):eaay0688. doi: 10.1126/science.aay0688. Epub 2020 Mar 26.

3. <u>Structural and functional studies of antiviral drug toxicity</u>

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 □. 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 □□holoenzyme.

Recently, we determined structures of ternary complex of Pol □-DNA with a substrate or an antiHIV reagent, zalcitabine, lamivudine or emtricitabine. These structures provided unprecedented insight in Pol □□mediated antiviral drug toxicity. As Pol □□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, **Proc Natl Acad Sci USA***,* 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. ***J Am Chem Soc***. 2019, 141(27):10821-10829.

4. <u>Studies of tryptophanyl tRNA synthetase fidelity</u>

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 aim 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 Å crystal structure of tryptophanyl-tRNA synthetase complexed with ATP in a closed, pre-transition-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

D. Research Support

Ongoing Research Support

R01 AI134611 Yin (PI) 03/01/2018-02/28/2023
National Institutes of Health
Structural Basis for Antiviral Drug Mitochondrial Toxicity
The goal of the study is to illustrate mechanisms for mitochondrial antiviral drug toxicity that designed to treat HIV and HCV coinfection. We focus on revealing differentiate nucleoside analogs interaction between viral target and human adverse reaction targets using structural biology, enzymology and medicinal chemical approaches.

R01 NS095747 (PI: Tang) 09/30/2016-08/31/2021
NIH/NINDS (Yin Role: co-I)
Antiretroviral therapy and neuroinflammation in CNS
The goal of the study is to understand HIV-associated neurological disorders such as neuropathic pain and neurocognitive deficits. My role is to advise on drug toxicity.
The project has no overlap with the pending grant.

R01 AI136031 (PI: Garg) 09/25/2017-08/31/2022
NIH/NIAID (Yin Role: co-I)
Oxidative response networks in Chargus cardiomyopathy
The goal of the project is investigate PARP1 cross-talk with mitochondrial DNA polymerase G (POLG) and its effects on mtDNA integrity in cardiomyocytes and chagasic heart.

Completed Research Support

R01 110591 Yin (PI) 03/01/2014-02/28/2018
National Institutes of Health
Dissecting dual function of Pol gamma in mtDNA replication and oxidative damage repair.
The goal of the study is to Pol gamma participates two different processes by association with different accessory proteins.