BIOGRAPHICAL SKETCH

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NAME: Liujie Wang (Jeff)

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

POSITION TITLE: MD/PhD Student

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)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
University of California Los Angeles, CA	B.S/M.S.	09/2013	06/2017	Biochemistry
UT Health San Antonio, TX	M.D./Ph.D.	05/2019	05/2028 (expected)	Biochemistry/Medicine

A. Personal Statement

My long-term career goal is to train and become a physician-scientist working at the interface of clinical oncology and mechanistic cancer biology as an independent investigator. Growing up in an academic household, I developed a penchant for science through my exposure to chemistry and biology courses during my secondary education, which ultimately led to me to pursue my undergraduate studies in biochemistry. After my first years of biochemistry coursework, I was eager to apply my conceptual knowledge to tackle a research project. I sought out undergraduate research opportunities in the biochemistry department and shortly thereafter began as a student researcher in the lab of Dr. Margot Quinlan. There, I investigated the regulatory role of Formin proteins and Rab GTPases on actin microfilaments in facilitating proper cellular polarity during oogenesis. I further developed this project into a master's thesis during the final year of my undergraduate tenure. Through my work in the lab and interfacing with various other research topics from the countless seminars offered on campus, I gained a deeper understanding and appreciation for the sheer amount of crosstalk between basic and translational biomedical research and its overall impact on medicine. The culmination of my undergraduate research experiences taught me to generate testable scientific hypotheses, trained me to design appropriate experiments to address my research hypotheses, introduced me to the intricate workings of a research lab, and helped me crystallize my interest in pursuing a career as a physician-scientist.

To further strengthen myself in preparation for MD/PhD applications, I took two gap years to work as a research associate/lab manager in the lab of Dr. Sriram Kosuri in the Department of Chemistry and Biochemistry at UCLA. The transition took me from actin protein biochemistry to the implementation of NGS-based high throughout DNA-barcode-based reporter assays to interrogate several biological questions specifically, GPCR-ligand response and splicing. In doing so, I helped write several supplemental sections in the subsequent publications on this work, which allowed me to further hone my written scientific communication skills. Through this experience, I further developed my skills in hypothesis and experimental design and gained exposure to bioinformatics and new experimental techniques. The culmination of my research tenure at UCLA solidified my interest to pursue further training through an M.D./Ph.D. Program. I believed that the physician-scientist track would train me to address research questions through the lens of a clinician to better translate bench discoveries to the bedside.

In May 2019, I matriculated into the M.D./Ph.D. program at UT Health San Antonio. During the first two pre-clinical years of medical school, I developed a strong interest in cancer biology and was fortunate to rotate and ultimately join the lab of Dr. Patrick Sung in June 2021 for my Ph.D. studies. With the support of the competitive institutional cancer biology T32 training program, I am excited to explore and mature as a scientist in the field of DNA repair with a strong emphasis on characterizing the molecular mechanisms of the repair machinery within the larger cellular context of genome instability and cancer progression. In addition, I will not only receive rigorous training as a scientist but also develop my clinical skills following my graduate research studies when I return to

finish my medical school training. The proposed goals of this fellowship would further strengthen my training in biomedical research and medicine and robustly prepare me for the next stage of my training as a physician-scientist in the cancer biology field.

B. Positions, Scientific Appointments and Honors

Positions and Employment

2021-Present Graduate Student Researcher with Patrick Sung, D.Phil., UT Health San Antonio
2019-Present MSTP Candidate, UT Health San Antonio
2017-2019 Research Associate with Sriram Kosuri, Sc.D., UCLA
2015-2017 Undergraduate Research Student in Biochemistry with Margot Quinlan, Ph.D., UCLA

Other Experience and Professional Memberships

2022-Present Member, Mays Cancer Center, UT Health San Antonio, San Antonio, TX
2021-2022 Organizing Committee, 2022 South Regional APSA Meeting
2021-2022 APSA Student Mentor
2019-Present Member, American Physician Scientists Association (APSA)
2019-2021 Member, Oncology Student Association, UT Health San Antonio, San Antonio, TX

Academic and Professional Honors

2024 3MT Award, STX-MSTP Spring Retreat, UT Health San Antonio
2023 3rd Place Poster Award, STX-MSTP Spring Retreat, UT Health San Antonio
2023 1st Place, Poster Presentation: Mays Cancer Center Annual Retreat, UT Health San Antonio
2022- Cancer Biology T32 Training Program, UT Health San Antonio
2022 Hibbs Travel Award, Department of Biochemistry & Structural Biology, UT Health San Antonio
2020-2021 Long Scholar, UT Health San Antonio
2017 *Cum Laude*, Bachelor of Science, UCLA
2017 Master's Thesis in Chemistry and Biochemistry with Margot Quinlan Ph.D., UCLA
2017 Oral Talk Winner: Biochemistry Section, ACS-SCURC, Los Angeles, CA
2016-2017 Departmental Scholars Program, UCLA
2015 Whitcome Summer Research Fellowship, Department of Chemistry and Biochemistry, UCLA
2015 Undergraduate Research Fellowship Program, UCLA
2013-2017 Dean's List (Top 25% of Students), UCLA

C. Contributions to Science

2015-2017: Testing the protein-protein interaction of Drosophila Spire and Drosophila Rab GTPases. UCLA, CA

This undergraduate work in the lab of Dr. Margot Quinlan focused on teasing apart potential protein interactions between Drosophila Spire and Rab GTPases and their implication in polarity establishment during Drosophila oogenesis. As an actin binding protein, Spire facilitates actin polymerization, a critical cellular process enabling motility, trafficking, and signal conduction. Rabs are a group of molecular switches implicated in various functional pathways including actin dynamics. Preliminary in vitro data from my master's thesis showed varied binding strengths of three Rab GTPases, Rab3, Rab5, and Rab11 for Spire. Concurrently, I generated partial Spire knockout strains of Drosophila to test the importance of its Rab binding domain for proper polarity control in oogenesis, which is critical during early developmental biology. This early work establishes a foundation for further investigation of novel binding interactions between Spire and Rab GTPases and their mechanistic role in various actin related processes. The culmination of this work led to an oral talk at the 2017 ACS-Southern California Undergraduate Research Conference and the completion of my master's thesis.

a. Wang, L. (2017). Interaction Between Spire and Rab GTPases and its Effect on the Developing Drosophila Oocyte. UCLA. ProQuest ID: Wang_ucla_0031N_16237. Merritt ID: ark:/13030/m5033nbw. Retrieved from https://escholarship.org/uc/item/5hv5d87j

b. Wang, L, Quinlan, M. Protein interaction between Drosophila Spire and Rab GTPases. ACS-Southern California Undergraduate Research Conference, UCLA, Los Angeles, CA. 2017. Talk

c. Wang, L, Quinlan, M. Protein interaction between Drosophila Spire and Rab GTPases. UCLA Undergraduate Research Week, UCLA, Los Angeles, CA. 2016. Poster

2017-2019: Engineering synthetic cellular reporter assay system for interrogation of receptor-agonist activation. UCLA, CA

This project in the Kosuri lab focused on interrogating the odorant space of murine olfactory receptors (MOR), a type of G-protein coupled receptor (GPCR), via an engineered reporter assay leveraging high-throughput sequencing technology to quantify receptor activation through the proxy of a unique DNA barcode identifier.

Much of the chemical space of both murine and human olfactory receptors is currently still under characterized. Mapping these chemical connections will indelibly enhance our understanding of the neurocircuitry of MORs as well as the biochemical specificity of agonist activation by GPCRs. Traditional methods of eliciting receptor activation through chemiluminescent based assays have major throughput restraints. Hence, we engineered a multiplexed cellular reporter assay that exploited next-generation sequencing (NGS) technology to quantify receptor-agonist activation. The reporter platform used a plasmid based synthetic circuit that was stably integrated into a HEK293T cell line. This synthetic circuit consisted of a library of MOR genes, driven by an inducible Tet-promoter, and a cAMP response element driven reporter gene containing a unique DNA molecular identifier that was previously mapped to a specific MOR. Once integrated into the HEK293T cell line, the addition of tetracycline drove expression of each MOR. Subsequent agonist activation elicited the signaling cascade from the MOR to adenylate cyclase, to cAMP activation which drove transcription of the reporter gene. Agonist activation can then be quantified by measuring the number of reporter transcripts with the unique DNA molecular identifier and mapped back to the corresponding MOR. Through an iterative approach, I engineered and tested different numbers of cAMP response element sites upstream of the reporter sequence, which allowed for tuning the downstream reporter transcription signal in response to the agonist molecule. My work in sequence optimization of this cellularly integrated reporter system helped demonstrate the initial proof of concept for testing receptor agonist activation in a high-throughput manner. This work opens the door for future testing of receptor libraries against a large chemical profile at scale.

a. Jones, E.M., Jajoo, R., Cancilla, D., Lubock, N.B., **Wang, J.,** Satyadi, M., Cheung, R., March, C., Bloom, J.S., Matsunami, H., Kosuri, S. (2019). A Scalable Multiplexed Assay for Decoding GPCR-Ligand Interactions with RNA Sequencing. Cell Systems, 8(3), 254-260. PMCID: PMC6907015

2017-2019: Engineering synthetic cellular reporter assay system for deep mutational scanning of the Beta2-Adrenergic Receptor. UCLA, CA

This project in the Kosuri lab leveraged the reporter assay platform for assessing MOR agonist activation in the previous section with a few modifications to conduct a deep mutational scan (DMS) of the Beta2-adrenergic receptor (ADRB2) in response to isoproterenol, a major agonist. DMS allowed for systematic dissection of protein residue conservation that is critical for enzymatic function. The synthetic circuit deployed in this study consisted of a library of the Beta2 adrenergic receptor coding sequence mutated at each amino acid position to the 19 other amino acids and a library of DNA barcodes just downstream of the reporter gene. Initial sequencing allowed for mutant ADRB2 variants to DNA barcode mapping. Subsequent isoproterenol addition and differential activation of the mutant ADRB2 variants were quantified by the level of DNA barcodes measured by next-generation sequencing which served as a proxy for agonist activation. Differential receptor activation would lead to differential reporter transcription and ultimately different levels of DNA barcodes that can mapped back to the ADRB2 mutant variant of interest. This work not only corroborated previously characterized structural data and key residues for signaling but also revealed an uncharacterized structural latch spanning the first two extracellular loops that are highly conserved across Class A G-protein coupled receptors. Again, the work specifically demonstrated initial proof of concept of our reporter platform for dissecting the protein sequence space of the beta-2-adrenergic receptor. Furthermore, through several individual mutant residue testing, I validated our report assay data on a novel highly conserved structural latch motif spanning the first two extracellular loops of the receptor. This system could readily be deployed to test other GPCRs to characterize key residue candidates for further downstream functional mutation studies.

a. Jones, E.M., Lubock, N.B., Venkatakrishnan, A.J., **Wang, J.,** Tseng, A.M., Paggi, J.M., Latorraca, N.R., Cancilla, D., Satyadi, M., Davis., J.E., Babu, M.M., Dror, R.O., Kosuri, S. (2020). Structural and functional characterization of G protein-coupled receptors with deep mutational scanning. eLife. PMCID: PMC7707821

2017-2019: Engineering a multiplexed minigene reporter assay for functional splicing assessment of human genetic variants. UCLA, CA

This project in the Kosuri lab explored how human genetic variants affected exon recognition using a multiplexed functional assay of splicing via Sort-Seq (MFASS). Differential splicing effects have broad implications in cellular gene expression and can induce large perturbation effects within the cell. Some of these effects invariably lead to disease states. Thus, we wanted a comprehensive understanding of the human genetic variants surrounding exonic regions and their potential effects on splicing. The platform deployed in this study utilized a split GFP minigene containing a synthetic exon library flanked by consensus intronic regions. The designed exon library contained variants of interests within or adjacent to 2198 human exons curated from the Exome Aggregation Consortium. This minigene was then stably integrated into HEK293T cells and subsequently sorted for GFP signal. Variants that caused exon skipping led to reconstitution of the GFP gene and a greater GFP signal while variants that caused exon inclusion had minimal GFP signal. Post sort sequencing allowed for identification of

variants and their relative effects on exon recognition based on the relative abundance of transcripts containing the variant sequence of interest. Furthermore, I individually tested a group of exon variants within their native sequence context to validate the high throughput minigene reporter assay data. The data revealed that a small fraction of the variants, most of which are extremely rare, generated large splicing effects. Further exploration within the clinical variant databases could reveal new insight into disease states induced by splicing defects.

a. Cheung, R., Insigne, K.D., Yao, D., Burghard, C.P., **Wang, J.,** Hsiao, Y.E, Jones, E.M, Goodman, D.B., Xiao, X., Kosuri, S. (2019). A Multiplexed Assay for Exon Recognition Reveals That an Unappreciated Fraction of Rare Genetic Variants Cause Large-Effect Splicing Disruptions. Molecular Cell, 73(1), 183-194. PMCID: PMC6599603

2021-Present: Investigating the function role of the MCM8-9 helicase complex in HR repair. UT Health San Antonio, TX

I am currently investigating the functional mechanism of the obligate dimeric helicase complex MCM8-9 in Homologous Recombination (HR) mediated repair of DNA double-strand breaks. This research strives to advance our understanding of how the MCM8-9 helicase complex along with its effector protein, MCM8IP, biochemically mediates genome stability maintenance through its likely role in the repair DNA synthesis step of HR, and to understand how clinically relevant cancer-associated mutations within MCM8-9 impact DNA repair. We postulate a functional role of the MCM8-9 helicase complex and its stimulatory factor, MCM8IP to unwind D-loop structures to facilitate Pol-delta-mediated repair DNA synthesis. Currently, I have expressed and purified the components of MCM8IP, MCM8-9, and RAD51 to near homogeneity over several purification preparations and have functionally verified the ATPase and helicase activity of the MCM8-9 complex. In addition, I have demonstrated preferential DNA unwinding activity of MCM8-9 for 5' invading strands using a short oligo-based D-loop substrate. This suggests a potential function of MCM8-9 to unwind incorrectly oriented invading strands during D-loop formation to allow reinvasion of the RAD51-coated single-strand DNA (ssDNA) in the correct direction. This provides the biological context and the project roadmap as I progress through this proposal.

a. Wang J, Rogers C, Kwon Y, Sung P. Functional characterization of the MCM8-9 helicase complex in HR repair. Mays Cancer Center Annual Research Symposium, UT Health San Antonio, San Antonio, TX. February 2023 and 2024.

b. Wang J, Rogers C, Kwon Y, Sung P. Functional characterization of the MCM8-9 helicase complex in HR repair. Annual Greehey Children's Cancer Research Institute Retreat, UT Health San Antonio, San Antonio, TX. November 2023.

c. Wang J, Rogers C, Kwon Y, Sung P. Functional characterization of the MCM8-9 helicase complex in HR repair. Cancer Biology Training Consortium Annual Retreat, San Antonio, TX. October 2022.

d. Wang J, Rogers C, Kwon Y, Sung P. Functional characterization of the MCM8-9 helicase complex in HR repair. South Texas MSTP Annual Retreat, UT Health San Antonio, San Antonio, TX. April 2022, 2023, 2024

e. Wang J, Rogers C, Kwon Y, Sung P. Functional characterization of the MCM8-9 helicase complex in HR repair. 2022 American Physician Scientists Association (APSA) South Regional Meeting (Virtual). February 2022.

D. Scholastic Performance

YEAR	COURSE TITLE	GRADE	YEAR	COURSE TITLE	GRADE
University of California Los Angeles					
2013	Introductory Statistics	A	2015	Biochemical Methods I	A-
2013	General Chemistry I	A+	2015	Elementary Particles-Universe	A
2013	Calculus I	A	2015	Research Apprenticeship	P
2013	Biology I	A-	2015	From Scientific to Industrial Revolution	A
2013	General Chemistry II	A	2015	Research Apprenticeship	P
2013	Stars Galaxies Universe	A-	2015	Student Research Forum	P
2013	Calculus II	A	2015	Literature-20th Century Enlightenment	B+
2013	Biology II	A	2015	Thermodynamics	A-
2013	General Psychology	A-	2015	Cell Biology	A
2013	Multivariable Calculus	A-	2015	Biochemical Methods II	A
2014	General Chemistry III	A	2015	Protein Modifications	A
2014	Macroeconomics	A	2015	Introduction to Visual Culture	A-
2014	Biology III	B+	2015	Research Apprenticeship	P
2014	Organic Chemistry I	A+	2016	Jerusalem-Holy City	A-
2014	Organic Chemistry I Lab	A-	2016	Physical Biochemistry	A

2014	Vector Analysis	A-	2016	Introductory Sociology	A-
2014	Organic Chemistry II	A+	2016	History of Asian Americans	A-
2014	Organic Chemistry II Lab	A+	2016	Structural Molecular Biology	A
2014	Microeconomics	A+	2016	Structural Molecular Biology Lab	A
2014	Word Roots	A	2016	Introduction to Philosophy of Science	B+
2014	Linear Algebra	A	2016	Biochemistry Research Seminar	A
2014	Organic Chemistry III	A	2016	Protein Structure	B
2014	Organic Chemistry III Lab	A-	2016	Gene Expression	B+
2014	Differential Equations	A-	2016	Biomolecular Structure and Regulation	A
2014	Physics I	A	2016	Research-Master Thesis	A
2014	Physics II	A	2016	Biocatalysts and Bioengineering	A
2014	Lab and Scientific Method	B+	2016	Nucleic Acids Structures	A
2014	Biochemistry I	B+	2016	Cytoskeleton Dynamics	P
2014	Inorganic Chemistry I	A	2017	Research-Master Thesis	A
2014	Molecular Biology	B	2017	Biochemistry Research Seminar	A
2015	Biochemistry II	A	2017	Introductory Microbiology	B
2015	Genetics	A	2017	Research-Master Thesis	A
2015	Introductory Virology	A	2017	Ethics-Biomedical Research	P
2015	Biochemistry III	A	2017	Cytoskeleton Dynamics	P
2015	Protein Structure Biology	A	2017	Biochemistry Research Seminar	A
2015	Advanced Inorganic Chemistry	A	2017	Gene Regulation	A-
2015	Physics III	A			
YEAR	COURSE TITLE	GRADE	YEAR	COURSE TITLE	GRADE
UT Health San Antonio Medical School					
2019	Molecules to Medicine	HP	2020	Mind, Brain, Behavior	P
2019	Language of Medicine	P	2020	Medicine, Behavior, Society	H
2019	Attack and Defense	P	2020	Endocrine and Female Reproductive	P
2020	Hematology	HP	2020	Digestive Health and Nutrition	HP
2020	Respiratory Health	P	2021	Form and Function	HP
2020	Renal and Male Reproductive	P	2021	Clinical Skills	HP
2020	Cardiology	HP			
UT Health San Antonio Graduate School					
2021	Responsible Conduct of Research	S	2022	Qualifying Exam	H
2021	Scientific Writing Development	A	2022	Programming for Data Science	S
2021	BMM Seminar	S	2022	BMM Seminar	S
2021	Student Journal Club	A	2022	Research	S
2021	Rigor and Reproducibility	A	2022	Student Journal Club	A
2021	Research	S	2023	Cancer Core 1	A
2022	Biophysical Methods	A	2023	Cancer Core 2	A
2022	Macromolecular Structure and Mechanism	A	2023	Genomic Data Analysis	A
2022	Exp Design/Data Analysis	A	2023	BMM Seminar	S
2022	BMM Seminar	S	2023	Research	A
2022	Research	S	2023	Student Journal Club	S
2022	Student Journal Club	A	2024	BMM Seminar	S
2023	BMM Seminar	S	2024	Student Journal Club	S
2023	Research	A	2024	Research	A
2023	Student Journal Club	S			

UCLA is graded as A+, A, A-, B+, B, B-, C+, C, C-, D+, D, D-, and F or alternatively on a P(pass)/F(fail) system. Passing is C and above, or non-letter grade of P.

UT Health San Antonio Medical School is graded on a H (Honors), HP (High Pass), P (Pass), F (Fail) system which corresponds to 4.0, 3.5, 3.0, 0.0 points on the standard GPA scale. Passing is P or better.

UT Health San Antonio Graduate School is graded as A, B, C, F scale. Non-letter grades are graded as H (Honors), S (Satisfactory), P (Pass), or U (Unsatisfactory). Passing letter grades are C or better, or passing non-letter grades of H, S, or P. Lastly, IP (In Progress).