BIOGRAPHICAL SKETCH

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NAME: Liu, Chang

eRA COMMONS USER NAME (credential, e.g., agency login): CHANG.LIU01

POSITION TITLE: Assistant 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
China Medical University, China	M.B.	07/2008	Clinical Medicine
Emporia State University, USA	M.S.	07/2011	Microbial and Cellular Biology
University of Minnesota, Twin Cities, USA	Ph.D.	05/2016	Coronavirus biology and structural biology
Yale University, USA	Postdoctoral	07/2022	Structural biology and Immunobiology

A. Personal Statement

I have a long-standing passion for understanding the molecular mechanisms and biological functions of the complex interplay between human and viral pathogens. Throughout my career, I have acquired extensive training and rich research experience in coronavirus biology, structural biology, immunology, protein-nucleic acid biochemistry, pharmacology, and genomics. As a graduate student with Fang Li at University of Minnesota, Twin Cities, I devoted myself to investigating the receptor recognition and cell entry mechanisms of coronaviruses. My pioneering work has elucidated the molecular mechanism that governs the cross-species transmission of Middle East respiratory syndrome coronavirus (MERS-CoV) and provides critical guidance for preventing and controlling the spread of emerging and re-emerging deadly human coronaviruses such as SARS-CoV-2. In addition, I was heavily engaged in determining the structure of MERS-CoV spike protein, which is regarded as the major target for antiviral intervention and the prime candidate for vaccine design. These intriguing studies strengthened my determination to further provide mechanistic insights into the dynamic virus-host interplay that governs the ultimate outcome of virus infection. To this end, after graduate school, I chose to join David Schatz's lab at Yale to broaden my expertise in immunobiology and deepen my understanding of how the host develops protective immunity to defend against invading pathogens. With the customized time-resolved cryo-electron microscopy (cryo-EM) sample preparation and data analysis pipeline I developed, my research yielded the first comprehensive structural description of an ancestral recombination-activating gene (RAG) family transposase and illuminated the structural and biochemical basis of the function and evolutionary of RAG recombinase, an enzymatic machine that initiates antigen receptor gene diversification and is critical for host antiviral immunity. Meanwhile, the ongoing crisis of the COVID-19 pandemic has motivated me to identify novel druggable targets to treat this deadly viral disease. My work has elucidated the molecular mechanism of mismatch recognition during coronavirus RNA synthesis, casting fresh light on the immune evasion mechanism of SARS-CoV-2 and laying the foundation for the development of novel highly effective anti-coronavirus strategies. My fruitful graduate and postdoctoral work has led to 18 publications including my first- and/or corresponding-authored papers in *Nature*, *Science,* and *Nature Reviews Immunology*. This project aims to develop novel conceptual frameworks and design new approaches and tools

to elucidate the emerging mechanisms of viral gene regulation and identify new promising druggable targets for innovative and effective antiviral treatments.

Recently completed projects that I would like to highlight include:

Richard K. Gershon and Francis Trudeau Fellowship, Yale University
Liu (PI)
09/01/2019-08/31/2020
Functional and structural characterization of an early RAG-like transposase

Citations:

(* denotes co-first authors, # denotes corresponding authors)

a. **Liu, C.***, Yang, Y.*, & Schatz, D.G. (2019). Structures of a RAG-like transposase during cut-and-paste transposition. ***Nature*** *575*(7783), 540-544.
b. Yang, Y.*,#, **Liu, C.*,#**, Zhou, W.*, Shi, W.*, Chen, M., Zhang, B., Schatz, D.G., Hu, Y.#, Liu, B.# (2021). Structural visualization of transcription activated by a multidrug-sensing MerR family regulator. ***Nat Commun*** *12*(1), 1-14.
c. **Liu, C.#**, Shi, W., Becker, S.T., Schatz, D.G., Liu, B.#, & Yang, Y.# (2021). Structural basis of mismatch recognition by a SARS-CoV-2 proofreading enzyme. ***Science*** 373(6559): 1142-1146.
d. **Liu, C.***, Zhang, Y.*, Liu, C., Schatz, D.G., (2022). Structural insights into the Evolution of the RAG Recombinase. ***Nat Rev Immunol*** 22, 353-370

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022 – Present	Assistant Professor, Johns Hopkins University, Baltimore, MD
2016 – 2022	Postdoctoral Associate, Yale University, New Haven, CT
2015 – 2016	Member, American Society for Virology
2011 – 2016	Graduate Research Assistant, University of Minnesota, Twin Cities, Minneapolis, MN
2011 – 2012	Member, American Society for Cell Biology
2011 – Present	Member, The Honor Society of Phi Kappa Phi
2009 – 2011	Graduate Research Assistant, Emporia State University, Emporia, KS
2010 – 2011	Member, Kansas Academy of Science

Honors

2024 Searle Scholar
2023 NIH/NIAID New Innovators Award
2022 Cancer Prevention & Research Institute of Texas (CPRIT), Declined
2019 Richard K. Gershon and Francis Trudeau Postdoctoral Research Fellowship, Yale University
2018 NVIDIA GPU grant, NVIDIA
2017 The James Hudson Brown - Alexander Brown Coxe Postdoctoral Fellowship, Yale University
2016 Dr. Marvin and Hadassah Bacaner Research Awards, University of Minnesota
2016 Veneziale-Steer Award, University of Minnesota
2016 Travel Award, 29th International Conference on Antiviral Research
2016 Doctoral Dissertation Fellowship Conference Presentation Grant, University of Minnesota
2015 Doctoral Dissertation Fellowship, University of Minnesota
2015 Veterinary Virology Club Travel Award, American Society for Virology
2015 Graduate Student Travel Award, University of Minnesota
2011 Graduate School Fellowship (Block Grant), University of Minnesota
2011 MS Second Place Poster Award, 143rd Kansas Academy of Science Meeting
2010 Katherine Smalley Graduate Scholarship, Emporia State University
2010 Travel Award, 50th Annual Meeting of the American Society for Cell Biology
2010 Graduate Student Research Grant - fall semester, Emporia State University
2010 Graduate Student Research Grant - spring semester, Emporia State University

2010 MS Second Place Poster Award, 142nd Kansas Academy of Science Meeting
2010 MS Third Place Poster Award, 142nd Kansas Academy of Science Meeting
2007 Outstanding Undergraduate Student Scholarship, China Medical University
2005 Outstanding Undergraduate Student Scholarship, China Medical University

C. Contributions to Science

1. **Mechanism of coronavirus RNA proofreading.** SARS-CoV-2 proofreading exoribonuclease (ExoN) excises nucleotide analogs from the viral RNA, rendering most antivirals in this class ineffective. This study is the first structural description of any coronavirus ExoN-RNA complex and elucidates the molecular mechanism of mismatch recognition, explaining the limited success of most nucleotide-based antivirals. Our findings provide critical insights into the development of novel ExoN-resistant anti-coronavirus agents. I am the first and co-corresponding author of the work. I conceived the project, designed the experiments, processed cryo-EM data, performed atomic model building and structural analyses, and wrote the paper.

    a. **Liu, C.#**, Shi, W., Becker, S.T., Schatz, D.G., Liu, B.#, & Yang, Y.# (2021). Structural basis of mismatch recognition by a SARS-CoV-2 proofreading enzyme. ***Science*** 373(6559): 1142-1146.

2. **Structure, function, and evolution of the RAG recombinase and RAG-like transposases.** The RAG recombinase, responsible for the diversification of antibodies and T-cell receptors, was believed to evolve from a transposase in the Transib superfamily. As a postdoc with David Schatz, my study reported a comprehensive series of crystal and cryo-EM structures of an active Transib transposase spanning the entire transposition cycle. These structures together reveal the reaction pathway of a eukaryotic cut-and-paste transposase in unprecedented detail and highlight the evolutionary adaptations that transformed the ancestral transposase into a RAG recombinase. The findings of my study also led to a review article that provides a comprehensive understanding of the evolution and molecular details of the domestication process of RAG-like transposase. I am the first author in the following publications.

    a. **Liu, C.***, Yang, Y.*, & Schatz, D. G. (2019). Structures of a RAG-like transposase during cut-and-paste transposition. ***Nature*** *575*(7783), 540-544.
        - *Featured in Nature News & Views: Snapshots of a genetic cut-and-paste*
        - *Recommended by F1000*
    b. **Liu, C.***, Zhang, Y.*, Liu, C., Schatz, D.G., (2022). Structural insights into the Evolution of the RAG Recombinase. ***Nat Rev Immunol*** 22, 353-370

3. **Mechanism of transcription activation:** The MerR family transcriptional regulators bind to myriad cellular signals, ranging from heavy metals to drug-like compounds, and activate the transcription of a wide range of genes involved in the metabolism of antibiotics and heavy metals. We have characterized the function and determined the atomic structure of a novel multidrug-sensing MerR family transcriptional regulator EcmrR. Additional nine cryo-EM structures reveal the EcmrR-dependent transcription process from promoter opening to transcription initiation to RNA elongation. Meanwhile, we have obtained the cryo-EM structures that depict transcription activation by a metal-responsive transcriptional regulator CueR. These two studies have been instrumental in yielding a comprehensive model for transcription regulation by the bacterial MerR family regulators, with broad mechanistic implications for multidrug resistance and metal homeostasis in bacteria. I am the co-first and/or co-corresponding author of these studies.

    a. Yang, Y.*,#, **Liu, C.*,#**, Zhou, W.*, Shi, W.*, Chen, M., Zhang, B., Schatz, D.G., Hu, Y.#, Liu, B.# (2021). Structural visualization of transcription activated by a multidrug-sensing MerR family regulator. ***Nat Commun*** *12*: 2702.
    b. Shi, W.*, Zhang, B.*, Jiang, Y.*, **Liu, C.***, Zhou, W., Chen, M., Yang, Y., Hu, Y., Liu, B. (2021). Structural basis of copper-efflux-regulator-dependent transcription activation. ***iScience*** *24*(5), 102449.

4. **Receptor recognition, cell entry, and cross-species transmission of coronaviruses.** The outbreaks of the Middle East respiratory syndrome coronavirus (MERS-CoV) and porcine epidemic diarrhea virus (PEDV) in 2012 and 2013, respectively, posed major threats to global health and led to substantial

economic loss. As a graduate student in Fang Li's lab, I took the initiative to elucidate the molecular underpinning of the receptor recognition, cell entry, and cross-species transmission of these two deadly coronaviruses. My work has led to the identification of a bat coronavirus, HKU4, as a close relative to MERS-CoV and provides fundamental insights into the cross-species transmission of coronaviruses. My subsequent work also revealed the mechanism of receptor recognition and cell entry mediated by the spike protein of PEDV, paving the way for the development of effective antiviral therapies targeting this essential viral component. I am the first or co-first author in all these studies.

a. Yang, Y.*, Du, L.*, **Liu, C.***, Wang, L., Ma, C., Tang, J., Baric, R. S., Jiang, S., Li, F. (2014). Receptor usage and cell entry of bat coronavirus HKU4 provide insight into bat-to-human transmission of MERS coronavirus. ***Proc Natl Acad Sci USA**, 111*(34), 12516-12521.
b. Yang, Y.*, **Liu, C.***, Du, L., Jiang, S., Shi, Z., Baric, R. S., Li, F. (2015). Two mutations were critical for bat-to-human transmission of Middle East respiratory syndrome coronavirus. ***J Virol**, 89*(17), 9119-9123.
c. **Liu, C.***, Tang, J.*, Ma, Y.*, Liang, X., Yang, Y., Peng, G., Qi, Q., Jiang, S., Li, J., Du, L., Li, F. (2015) Receptor usage and cell entry of porcine epidemic diarrhea coronavirus. ***J Virol*** 89: 6121-6125.
d. **Liu, C.***, Ma, Y.*, Yang, Y.*, Zheng, Y., Shang, J., Zhou, Y., Jiang, S., Du, L., Li, J., Li, F. (2016) Cell Entry of Porcine Epidemic Diarrhea Coronavirus Is Activated by Lysosomal Proteases. ***J Biol Chem*** 291: 24779-24786

5. **Structural and functional diversity of coronavirus spike protein.** Coronavirus spike proteins represent a model system to study viral protein evolution because of their substantial structural and functional diversity across different genera. This body of work led to the determination of the first cryo-EM structures of the spike protein trimer from γ- and δ-coronavirus, respectively, as well as the cryo-EM structure of a β-coronavirus spike protein trimer in complex with its cellular receptor. These structures provide the critical missing pieces for understanding the structural and functional diversity of coronavirus spike proteins among different genera and shed light on the evolution of this highly divergent cell-invading molecular machinery. I was the co-first author in one of these studies and was heavily engaged in the processing and analysis of the cryo-EM structures in the other two studies.

a. Shang, J., Zheng, Y., Yang, Y., **Liu, C.**, Geng, Q., Tai, W., Du, L., Zhou, Y., Zhang, W., Li, F. (2018) Cryo-Electron Microscopy Structure of Porcine Deltacoronavirus Spike Protein in the Prefusion State. ***J Virol*** 92: e01556-17
b. Shang, J., Zheng, Y., Yang, Y., **Liu, C.**, Geng, Q., Luo, C., Zhang, W., Li, F. (2018) Cryo-EM structure of infectious bronchitis coronavirus spike protein reveals structural and functional evolution of coronavirus spike proteins. ***PLoS Pathog*** 14: e1007009
c. Shang, J.*, Wan, Y.*, **Liu, C.***, Yount, B., Gully, K., Yang, Y., Auerbach, A., Peng, G., Baric, R.S., Li, F. (2020). Structure of mouse coronavirus spike protein complexed with receptor reveals mechanism for viral entry. ***PLoS Pathog*** 16: e1008392

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/chang.liu.11/bibliography/public/