BIOGRAPHICAL SKETCH

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NAME: Jun Wang

eRA COMMONS USER NAME (credential, e.g., agency login): JUNW912

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
Wuhan University, Wuhan, China	BS	06/2003	Chemistry
National University of Singapore, Singapore	MSc	06/2006	Chemical Biology
University of Pennsylvania, Philadelphia, PA	PhD	12/2010	Organic Chemistry
University of Pennsylvania, Philadelphia, PA	Postdoc	10/2011	Biochemistry and Biophysics
University of California, San Francisco, San Francisco, CA	Postdoc	02/2014	Pharmaceutical Chemistry

A. Personal Statement

I am an Associate Professor at the Department of Medicinal Chemistry, Rutgers Ernest Mario School of Pharmacy. The central themes of my research have been the discovery of novel antiviral drug target and studying the mechanism of drug resistance. The proposed studies are built upon our long-term interest in developing antivirals targeting the non-polio enteroviruses (NPEVs). Among the NPEV antivirals we discovered, the 2C inhibitors are the most promising ones showing broad-spectrum antiviral activity and nanomolar potency. In this project, we propose to develop broad-spectrum NPEV antivirals against EV-D68 and EV-A71 with *in vivo* antiviral efficacy in mouse models. In addition, we will solve the X-ray structures of 2C with structurally disparate 2C inhibitors. We are in a unique position to tackle this problem and we have all the necessary expertise and resources in place including the EV-A71 and D68 reverse genetics systems, 2C binding assay, and the lead 2C inhibitors with favorable PK properties and *in vivo* antiviral efficacy.

I have been studying antivirals in the past 17 years. For influenza virus, we have made progress in designing inhibitors targeting the M2 proton channel and viral polymerase PA-PB1 interactions, and our work has been highlighted by Scientific American and Nature. For enteroviruses, we have designed inhibitors against several viral proteins including the VP1 capsid protein, the 2A and 3C proteases, the 2C protein and the 3D viral polymerase. The 2C inhibitors we designed are among the first small molecules showing *in vivo* antiviral efficacy against EV-D68 in mouse model. For coronaviruses, we are developing inhibitors targeting the SARS-CoV-2 main protease (M^{pro}) and papain-like protease (PL^{pro}) with novel reactive warheads and a high target specificity. Over the years, my group has accumulated broad expertise in parallel protein production, assay development, high-throughput screening, structure-based drug design, PK optimization, pharmacology, and virology. These experiences pave the way for the proposed studies and make me well qualified for this grant.

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

R01AI158775
Wang (PI)
08/01/2021-07/31/2026
Development of dual inhibitors targeting the viral main protease and the host cathepsin L as SARS-CoV-2 antivirals

R01AI157046
Wang (PI)

09/22/2020-08/31/2025
Drug target validation of the enterovirus D68 2A protease

R01AI147325
Wang (PI)
06/07/2019-05/31/2023
High-throughput Screening of Inhibitors Targeting the Enterovirus A71 and D68 2A proteases

Citations:

1. Hu Y, Kitamura N, Musharrafieh R, Wang J.* (2021) Discovery of Potent and Broad-Spectrum Pyrazolopyridine-Containing Antivirals against Enteroviruses D68, A71, and Coxsackievirus B3 by Targeting the Viral 2C Protein. ***J. Med. Chem.*** 64, 8755-8774. PMID: 34085827; PMCID: PMC9179928.
2. Musharrafieh, R., Zhang, J.T., Tuohy, P., Kitamura, N., Bellapalli, S.S., Hu, Y.M., Khanna, R., and Wang, J.* (2019) Discovery of quinoline analogous as potent antivirals against enterovirus D68 (EV-D68). ***J. Med. Chem.*** 62, 4074-4090. PMCID: PMC8055447.
3. Ma C, Xia Z, Sacco M, Hu Y, Townsend J, Meng X, Choza J, Tan H, Jang J, Gongora M, Zhang X, Zhang F, Xiang Y, Marty M, Chen Y,* **Wang J.*** (2021) Discovery of di- and trihaloacetamides as covalent SARS-CoV-2 main protease inhibitors with high target specificity. ***J. Am. Chem. Soc.*** 143, 20697-20709. PMID: 34860011; PMCID: PMC8672434.
4. Sacco M, Ma C, Lagarias P, Gao A, Townsend J, Meng X, Dube P, Zhang X, Hu Y, Kitamura N, Hurst B, Tarbet B, Marty M, Kolocouris A, Chen Y,* Wang J.* (2020) Structure and inhibition of SARS-CoV-2 main protease reveals strategy for developing dual inhibitors against Mpro and cathepsin L. ***Sci. Adv.*** 6, eabe0751. PMID: 33158912; PMCID: PMC7725459.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

Editorial board	Medicinal Research Reviews, European Journal of Pharmaceutical Sciences, Acta Pharmaceutica Sinica B
Associate Editor	Journal of Medical Virology
Guest editor	PNAS, Plos Pathogens, International Journal of Molecular Sciences
2022-present	Associate Professor, Department of Medicinal Chemistry, Ernest Mario School of Pharmacy, Rutgers, the State University of New Jersey, Piscataway, NJ
2020-2021	Associate Professor, Department of Pharmacology and Toxicology, College of Pharmacy, University of Arizona, Tucson, AZ
2022	Reviewer, NIH ZRG1 F07C-M (20) L, Fellowships: Infectious Diseases and Immunology. 07/13/2022-07/14/2022
2022	Reviewer, NIH ZRG1 AIDC (82), Special Emphasis Panel “Antiviral Drug Discovery and Mechanisms of Resistance”. 03/07/2022-03/08/2022.
2021	Reviewer, NIH ZRG1 F07A-H 20, Fellowship: Infectious Diseases and Immunology Panel A. 11/9/2021-11/10/2021.
2021	Reviewer, NIH Special Emphasis Panel “Exploration of Antimicrobial Therapeutics and Resistance” ZRG1 AIDC-B (82)
2020	Reviewer, NIH-NIAID Emergency Awards: Rapid Investigation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Coronavirus Disease 2019 (COVID-19) ZAI1 SB-X
2020	Reviewer, NIH-NIAID Emergency Awards: Rapid Investigation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Coronavirus Disease 2019 (COVID-19) ZAI1 AMC-W (M1)
2015	Chairperson of the Structural and Chemical Biology Section of the Cancer Chemistry Subcommittee of the 2016 AACR Program Committee
2014-2020	Assistant Professor, Department of Pharmacology and Toxicology, College of Pharmacy, University of Arizona, Tucson, AZ

Honors

2022	Invited speaker at the World Health Organization “Scientific strategies from recent

outbreaks to help us prepare for Pathogen X"

2019 A. Jay Gandolfi New Investigator Award, University of Arizona
2017 30th ICAR meeting travel award, Atlanta, US
2016 29th ICAR meeting travel award, San Diego, US
2011 Top reviewer in the pharmaceutical sciences section by Elsevier

C. Contributions to Science

1. My group is leading the efforts in developing antivirals against enterovirus D68 (EV-D68). EV-D68 is the etiological agent for the biennial outbreaks of acute flaccid myelitis (AFM). There is no antiviral or vaccine available for the prevention and treatment of EV-D68 infection. We are developing inhibitors targeting several viral proteins including the capsid protein VP1, the viral proteases 2A and 3C, and viral 2C protein. The goal is to design potent and selective inhibitors as chemical probes for target validation (*in vitro* and *in vivo*) as well as drug candidates for translational research.
   a. Hu Y, Musharrafieh R, Zheng M, Wang J. Enterovirus D68 Antivirals: Past, Present, and Future. ***ACS Infect Dis.*** 2020 Jul 10;6(7):1572-1586. PMCID: PMC8055446.
   b. Ma, C.L., Zhang, J., Hu, Y.M., Musharrafieh, R., and Wang, J.* (2019) A novel capsid binding inhibitor displays potent antiviral activity against enterovirus D68. ***ACS Infect. Dis.*** 5, 1952-1962. PMCID: PMC7167248
   c. Musharrafieh, R., Zhang, J.T., Tuohy, P., Kitamura, N., Bellapalli, S.S., Hu, Y.M., Khanna, R., and Wang, J.* (2019) Discovery of quinoline analogous as potent antivirals against enterovirus D68 (EV-D68). ***J. Med. Chem.*** 62, 4074-4090. PMCID: PMC8055447.
   d. Musharrafieh, R.G., Ma, C., Zhang, J., Hu, Y., Diesing, J.M., Marty, M.T., and Wang, J.* (2019) Validating enterovirus D68-2A^{pro} as an antiviral drug target and the discovery of telaprevir as a potent D68-2A^{pro} inhibitor. ***J. Virol.*** 93, e02221-18. PMCID: PMC6430540.

2. Understanding the mechanism of antiviral drug resistance is vital in validating the mechanism of action and designing antivirals with a high genetic barrier to drug resistance. For influenza M2-S31N proton channel blockers, we found that resistance evolution is cell-type and virus strain dependent and discovered novel allosteric drug resistant mutants including R45H and L46P. For SARS-CoV-2 main protease, we found that the predominant Omicron mutant P132 remains sensitive to nirmatrelvir. Our recent comprehensive characterization of 102 M^{pro} mutants identified several drug resistant hot spot residues, which has been broadly covered in news media including Science News.
   a. Hu Y, Lewandowski E, Tan H, Zhang X, Morgan R, Zhang X, Jacobs L, Butler S, Gongora M, Choy J, Deng X, Chen Y,* **Wang J.*** (2022) Naturally occuring mutants of SARS-CoV-2 main protease confer drug resistance to nirmatrelvir. ***BioRxiv.*** 2022.06.28.497978.
   b. Sacco M, Hu Y, Gongora M, Meilleur F, Kemp M, Zhang X, **Wang J,*** Chen Y.* The P132H mutant in the main protease of Omicron SARS-CoV-2 decreases thermal stability without compromising catalysis or small molecule drug inhibition. ***Cell Res.*** 32, 498-500. PMID: 35292745; PMCID: PMC8923085.
   c. Musharrafieh R, Lagarias P, Ma C, Hau R, Romano A, Lambrinidis G, Kolocouris A,* Wang, J.* (2020) Investigation of the drug resistance mechanism of M2-S31N channel blockers through biomolecular simulations and viral passage experiments. ***ACS. Pharmacol. Transl. Sci.*** 3, 666-675. PMID: 32832869; PMCID: PMC7432665.
   d. Musharrafieh R, Ma C, Wang J.* (2018) Profiling the in vitro drug resistance mechanism of influenza A viruses towards the AM2-S31N proton channel blockers. ***Antiviral Res.*** 153, 10-22. PMID: 29518414; PMCID: PMC5891360.

3. To address the urgent need of antivirals for COVID-19, we are developing antivirals by targeting the SARS-CoV-2 main protease and papain-like protease. Our efforts led to the discovery of novel covalent and non-covalent M^{pro} inhibitors. In collaboration with Dr. Yu Chen at USF, we solved multiple X-ray crystal structures of M^{pro} in complex with several covalent and non-covalent inhibitors. The discovery of potent non-covalent M^{pro} inhibitors with a high target specificity provides a new direction in SARS-CoV-2 antiviral development.
   a. Ma C, Xia Z, Sacco M, Hu Y, Townsend J, Meng X, Choza J, Tan H, Jang J, Gongora M, Zhang X, Zhang F, Xiang Y, Marty M, Chen Y,* **Wang J.*** (2021) Discovery of di- and trihaloacetamides as covalent SARS-CoV-2 main protease inhibitors with high target specificity. ***J. Am. Chem. Soc.*** 143, 20697-20709. PMID: 34860011; PMCID: PMC8672434.
   b. Kitamura N, Sacco MD, Ma C, Hu Y, Townsend JA, Meng X, Zhang F, Zhang X, Ba M, Szeto T, Kukuljac A, Marty MT, Schultz D, Cherry S, Xiang Y, Chen Y,* Wang J.* (2021) Expedited Approach toward the

Rational Design of Noncovalent SARS-CoV-2 Main Protease Inhibitors. ***J. Med. Chem.*** 65, 2848-2865. PMID: 33891389; PMCID: PMC8536799.

c. Ma, C., Sacco, M., Hurst, B., Townsend, J., Hu, Y., Szeto, T., Zhang, X., Tarbet, B., Marty, M., Chen, Y.,* Wang, J.* (2020) Boceprevir, GC-376, and calpain inhibitors II and XII inhibit SARS-CoV-2 viral replication by targeting the viral main protease. ***Cell Res.*** 30, 678-692. PMCID: PMC7294525.
d. Sacco MD, Ma C, Lagarias P, Gao A, Townsend JA, Meng X, Dube P, Zhang X, Hu Y, Kitamura N, Hurst B, Tarbet B, Marty MT, Kolocouris A, Xiang Y, Chen Y,* Wang J.* (2020) Structure and inhibition of the SARS-CoV-2 main protease reveal strategy for developing dual inhibitors against M(pro) and cathepsin L. ***Sci. Adv.*** 6(50), eabe0751. PMCID: PMC7725459.

4. We have designed the "first-in-class" inhibitors targeting the drug-resistant influenza A virus M2 proton channels including V27A, L26F, and S31N. The most potent inhibitor, M2WJ206, was the first reported inhibitor targeting the M2-V27A mutant with *in vivo* antiviral efficacy. Following the success of designing V27A inhibitors, we subsequently designed potent channel blockers targeting the predominant M2-S31N mutant. One of the most potent M2-S31N inhibitor, M2WJ332, is highly active against drug-resistant influenza A viruses, including the 2009 pandemic strains A/California/07/09 (amantadine resistant) and A/Texas/04/09 (amantadine and oseltamivir resistant). Significantly, we recently developed the second generation of M2-S31N inhibitors with favorable *in vitro* and *in vivo* pharmacokinetic properties and promising *in vivo* antiviral activity against both oseltamivir-sensitive and -resistant influenza A viruses.
   a. Wang, Y.X., Hu, Y.M., Xu, S.T., Zhang, Y.T., Musharrafieh, R., Hau, R.K., Ma, C.L., and Wang, J.* (2018) In vitro pharmacokinetic optimizations of AM2-S31N channel blockers led to the discovery of slow-binding inhibitors with potent antiviral activity against drug-resistant influenza A viruses. ***J. Med. Chem.*** 61, 1074-1085. PMCID: PMC6445276.
   b. Li, F., Hu, Y., Wang, Y., Ma, C.L., and Wang, J.* (2017) Expeditious lead optimization of isoxazole-containing influenza A virus M2-S31N inhibitors using the Suzuki-Miyaura cross-coupling reaction. ***J. Med. Chem.*** 60, 1580-1590. PMCID: PMC5967881.
   c. Wu Y, Canturk B, Jo H, Ma C, Gianti E, Klein ML, Pinto LH, Lamb RA, Fiorin G,* Wang J,* DeGrado WF.* (2014) Flipping in the pore: discovery of dual inhibitors that bind in different orientations to the wild-type versus the amantadine-resistant S31N mutant of the influenza A virus M2 proton channel. ***J. Am. Chem. Soc.*** 136(52):17987-95. PMCID: PMC4286326.
   d. Wang J, Wu Y, Ma C, Fiorin G, Wang J, Pinto LH, Lamb RA, Klein ML, Degrado WF. (2013) Structure and inhibition of the drug-resistant S31N mutant of the M2 ion channel of influenza A virus. ***Proc. Natl. Acad. Sci. U S A.*** 110(4):1315-20. PMCID: PMC3557100.

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