OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 01/31/2026)

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: Xu, Wei |
| eRA COMMONS USER NAME (credential, e.g., agency login): weixu3 |
| 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) | END DATE MM/YYYY | FIELD OF STUDY |
| Zhejiang University, Hangzhou, Zhejiang | BS | 06/2008 | Applied Biological Sciences |
| Texas Tech University, Lubbock, TX  Washington Univ. School of Medicine, St. Louis, MO  Washington Univ. School of Medicine, St. Louis, MO | PHD  Postdoc  Scientist | 10/2014  12/2018  09/2024 | Biology  Biomedical Sciences  Infectious Diseases |

### A. Personal Statement

As a first-year investigator at the Joan C. Edwards School of Medicine, Marshall University, I lead pioneering research on host-directed therapies to combat diabetic skin and soft tissue infections (DSSTIs). My work addresses how infection-induced hyper-NETosis (excessive neutrophil extracellular trap formation) drives chronic tissue damage in diabetic patients. I aim to develop precision therapies that restore immune balance and halt tissue destruction—a transformative approach to improving outcomes for high-risk population.

**Qualifications:**

1. Expertise in host-pathogen interactions: I have discovered bacterial immune evasion strategies, including how short-chain fatty acids suppress macrophage IL-10 production to dysregulate host tolerance. I have also demonstrated that hyper-NETosis directly exacerbates tissue damage in diabetic mouse models of SSTI. Key experiments with NET-deficient mice confirmed that reducing NETosis preserves tissue integrity without compromising bacterial clearance.
2. Translational therapeutic development: I have established robust *in vitro* to *in vivo* infection models and standardized protocols to induce hyper-NETosis, enabling high-throughput drug screening. Additionally, I identified a bacterial virulence factor that triggers hyper-NETosis, revealing a novel therapeutic target to disrupt polymicrobial infection.
3. Training in mechanistic biology: I leveraged single-cell RNA sequencing and bulk transcriptomics to map immune dysregulation in SSTIs. Current work focuses on how hyper-NETosis reshapes the microbiome and immune microenvironment to perpetuate chronic infection.
4. Scientific independence and commitment to high-impact research: As a principal investigator, I have received startup funds and published in top-tier journals such as *Nature Communications*. I lead interdisciplinary collaborations in drug screening and immunotherapeutic development, working closely with PIs at other universities as well as within Marshall.
5. Commitment to mentorship: I actively mentor trainees, fostering diversity in science through hands-on training. My mentorship philosophy emphasizes scientific rigor, innovation-driven inquiry, and translational research in infectious disease immunology.

With my expertise in immune modulation, polymicrobial pathogenesis, and a comprehensive suite of cutting-edge techniques, I am uniquely positioned to lead this project. This grant will catalyze the development of first-in-class therapies that recalibrate—rather than suppress—the immune response, offering a paradigm shift in diabetic infection management.

My Bibliography: <https://www.ncbi.nlm.nih.gov/myncbi/wei.xu.19/bibliography/public/>

### B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

|  |  |
| --- | --- |
| 2024 - | Assistant professor, Marshall University School of Medicine, Huntington, WV |
| 2020 - 2024 | Staff Scientist, Washington University School of Medicine, St. Louis, MO |
| 2014 - 2018 | Postdoctoral fellow, Washington University School of Medicine, St. Louis, MO |

Honors

|  |  |
| --- | --- |
| 2017 - 2018 | Stephen I. Morse Postdoctoral Fellowship, Washington University School of Medicine |
| 2014 | Summer Dissertation Research Scholarship, Texas Tech University |
| 2013 | Grants-In-Aid Award, Texas Tech University |
| 2012 | Excellent Doctoral candidate Scholarship, Texas Tech University |
| 2011 | Graduate Summer Scholarship, Texas Tech University |

### C. Contribution to Science

# Mitigating Tissue Damage during Skin and Soft Tissue Infections

During my work in Dr. Michael Caparon’s laboratory, I demonstrated that *S. pyogenes* employs its aerobic fermentation pathway to subvert host disease tolerance—a defense mechanism that preserves tissue integrity and function during infection—in severe skin infections. This manipulation specifically impaired the recruitment of IL-10-producing immune cells, including macrophages and neutrophils, thereby delaying wound healing and exacerbating tissue damage. My research further uncovered that pathogen-derived fermentation byproducts, particularly acetate and formate, disrupt host acetyl-CoA metabolism. This disruption caused dysregulation of lysine acetylation processes, which in turn suppressed IL-10 expression at infection sites. By targeting this metabolic vulnerability with a bacterium-specific pyruvate dehydrogenase (PDH) inhibitor, I successfully reduced infection-driven tissue damage in murine models. This approach highlights a novel therapeutic strategy that specifically disrupts pathogen metabolic adaptation without broad-spectrum antimicrobial effects, offering a promising alternative to traditional antibiotic interventions.

* 1. Xu W, Bradstreet TR, Zou Z, Hickerson S, Zhou Y, He H, Edelson BT, Caparon MG. Reprogramming aerobic metabolism mitigates *Streptococcus pyogenes* tissue damage in a mouse necrotizing skin infection model. *Nat Commun* 2025 Mar 15;16(1):2559. PubMed Central ID: PMC11910614.
  2. Zou Z, Singh P, Pinkner JS, Obernuefemann CLP, Xu W, Nye TM, Dodson KW, Almqvist F, Hultgren SJ, Caparon MG. Dihydrothiazolo ring-fused 2-pyridone antimicrobial compounds treat *Streptococcus pyogenes* skin and soft tissue infection. Sci Adv. 2024 Aug 2;10(31):eadn7979. PubMed Central PMCID: PMC11296344.
  3. Merriman JA, Xu W, Caparon MG. Central carbon flux controls growth/damage balance for *Streptococcus pyogenes*. PLoS Pathog. 2023 Jun;19(6):e1011481. PubMed Central PMCID: PMC10337930.

# Identify Role of Proteases in Catheter-Associated Urinary Tract Infections (CAUTI)

As a postdoctoral fellow in the laboratories of Drs. Scott Hultgren and Michael Caparon, I investigated the mechanistic role of bacterial proteases in catheter-associated urinary tract infections (CAUTI) caused by *Enterococcus faecalis*. My work established that the pathogen’s secreted protease system (GelE-SprE) is essential for fibrinogen degradation, biofilm formation, and nutrient acquisition, enabling persistent infection. By administering protease inhibitors in a murine CAUTI model, I achieved a significant reduction in bacterial proliferation, host inflammation, and systemic dissemination. Notably, I identified the cysteine protease inhibitor E64 as a promising therapeutic candidate. Treatment with E64 not only diminished bladder inflammation and bacterial burdens but also revealed an unexpected mechanism: E64 disrupts host-pathogen crosstalk by inhibiting caspase-1-dependent apoptosis and necrosis, thereby attenuating pro-inflammatory cytokine release (IL-1β, IL-6) and limiting bladder epithelial damage. Further studies demonstrated that E64 modulates host eosinophil activity, impairing their recruitment and pathogen-adjuvant functions. Complementary experiments with eotaxin, a chemokine regulating eosinophil trafficking, validated their critical role in infection control. Collectively, these findings position host and bacterial cysteine proteases as dual therapeutic targets to disrupt persistent CAUTI—a strategy that bypasses traditional antibiotics and mitigates risks of resistance.

1. Xu W, Chen J, McLellan LK, Flores-Mireles AL, Hunstad DA, Caparon MG. Host Cysteine Proteases Promote Severity of Catheter-Associated Urinary Tract Infection and Kidney Fibrosis. mBio. In-submission.
2. Molina JJ, Kohler KN, Gager C, Andersen MJ, Wongso E, Lucas ER, Paik A, Xu W, Donahue DL, Bergeron K, Klim A, Caparon MG, Hultgren SJ, Desai A, Ploplis VA, Flick MJ, Castellino FJ, Flores-Mireles AL. Fibrinolytic-deficiencies predispose hosts to septicemia from a catheter-associated UTI. Nat Commun. 2024 Mar 27;15(1):2704. PubMed Central PMCID: PMC10973455.
3. Xu W, Flores-Mireles AL, Cusumano ZT, Takagi E, Hultgren SJ, Caparon MG. Host and bacterial proteases influence biofilm formation and virulence in a murine model of enterococcal catheter-associated urinary tract infection. NPJ Biofilms Microbiomes. 2017;3:28. PubMed Central PMCID: PMC5673934.

# Unraveling the Molecular Mechanisms of Soft Tissue Infections by *Leishmania* Parasite

As a graduate student in Dr. Kai Zhang’s laboratory, I elucidated molecular mechanisms enabling *Leishmania* parasites to adapt to hostile host environments, with a focus on lipid metabolism—a cornerstone of their pathogenicity. My work centered on the parasite’s unique lipid biosynthesis pathways, which are critical for membrane integrity and resilience under stress. Through functional and biochemical studies, I identified four novel virulence-associated enzymes: inositol phosphosphingolipid phospholipase C-like, sterol C-14 demethylase, sterol methyltransferase, and cyclopropane fatty acid synthase. Mechanistically, these enzymes govern the synthesis of specialized membrane lipids that enhance parasite stress tolerance, evasion of host immune defenses, and establishment of infection in animal models. My findings not only expanded the known repertoire of *Leishmania* virulence factors but also revealed these lipid metabolic enzymes as druggable targets for antiparasitic therapy. By linking their activity to parasite survival and infectivity, my work provides a biochemical roadmap for developing inhibitors that disrupt membrane stability or stress adaptation—strategies that could circumvent existing drug resistance mechanisms. This research underscores the therapeutic potential of targeting lipid metabolism to combat intracellular pathogens with high clinical unmet need.

* 1. Mukherjee S, Moitra S, Xu W, Hernandez V, Zhang K. Sterol 14-α-demethylase is vital for mitochondrial functions and stress tolerance in *Leishmania major*. PLoS Pathog. 2020 Aug;16(8):e1008810. PubMed Central PMCID: PMC7462297.
  2. Xu W, Mukherjee S, Ning Y, Hsu FF, Zhang K. Cyclopropane fatty acid synthesis affects cell shape and acid resistance in *Leishmania mexicana*. Int J Parasitol. 2018 Mar;48(3-4):245-256. PubMed Central PMCID: PMC5844833.
  3. Xu W, Hsu FF, Baykal E, Huang J, Zhang K. Sterol biosynthesis is required for heat resistance but not extracellular survival in *Leishmania*. PLoS Pathog. 2014 Oct;10(10):e1004427. PubMed Central PMCID: PMC4207814.
  4. Xu W, Xin L, Soong L, Zhang K. Sphingolipid degradation by *Leishmania major* is required for its resistance to acidic pH in the mammalian host. Infect Immun. 2011 Aug;79(8):3377-87. PubMed Central PMCID: PMC3147570.

# Hyper-NETosis Drives Diabetic Skin Infection Severity and Polymicrobial Pathogenesis

My current research identifies hyper-NETosis as a key driver of diabetic skin and soft tissue infections (DSSTIs). In diabetic murine models, *S. aureus* and *S. pyogenes* produced larger lesions and higher bacterial burdens, with *S. pyogenes* causing non-healing ulcers characterized by polymicrobial dominance. Despite lower neutrophil counts, these ulcers exhibited excessive NETosis, implicating NET dysregulation in disease progression. Diabetic mice lacking PAD4 showed smaller lesions, faster healing, and reduced bacterial loads, confirming NET-mediated tissue damage. Moreover, polymicrobial infections—especially *S. pyogenes*–*E. coli* co-infection—exacerbated hyper-NETosis. These findings establish diabetic NET dysregulation destabilizes tissue barriers, promotes polymicrobial expansion, and fuels chronic inflammation, suggesting PAD4 targeting as a promising therapeutic strategy.

* 1. Xu W, Liu S, Olson BS, Rosen A, Kau A, Hickerson S, Caparon M. Diabetic hyperglycemia primes hyper-NETosis in skin and soft tissue infections. In-submission.