BIOGRAPHICAL SKETCH

NAME: Wuest, William

eRA COMMONS USER NAME: wwuest

POSITION TITLE: GRA Distinguished Investigator and Professor of Chemistry

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
University of Notre Dame	BS	05/2003	Chemistry/Business
University of Pennsylvania	PHD	08/2008	Organic Chemistry
Harvard Medical School	Postdoctoral Fellow	06/2011	Bioorganic Chemistry

A. Personal Statement

Scientific Overview: The Wuest research mission is centered on *Translational Chemical Biology*. The overarching goal of the group is to uncover new antibiotic targets and biological pathways in both bacteria and microbiome environments by leveraging organic synthesis and microbiology. Currently, we are pursuing several synthetic and biochemical projects targeting bacterial growth, biofilm processes, resistance mechanisms, and virulence. In conjunction, we are using microbiological approaches to discover new therapeutics, identify unprecedented biological targets, and test for biological activity. The group is highly interdisciplinary, having key external scientific collaborations, in addition to those at Emory University (Antibiotic Resistance Center, Cystic Fibrosis-Atlanta) permitting the expedited testing of compounds and evaluation of their mechanism of action. We have recently expanded our capabilities to specifically implement our tool compounds in complex microbiological settings to better understand the chemical underpinnings that specific species play in microbiomes. This work has led us toward the development of ultra-narrow spectrum agents that target either one species or genus to articulate the roles of each in these environments. Toward this end we have developed lead compounds for commercialization, and in one case, started a company. Recent work from our laboratory has clearly demonstrated that we are one of the leaders in the field of natural product total synthesis of antibiotics. We have published over 130 papers since 2014 – most specifically related to the role natural-products (or analogs thereof) play in complicated microbiome environments. We continue to excel as an interdisciplinary, collaborative team of researchers centrally focused on better understanding bacterial processes in these settings.

Community Involvement: Throughout my career, I have been active in the chemistry community as a member of the ACS (bioorganic, organic, and medicinal chemistry divisions) and as a reviewer for these journals. I have served as a reviewer for all major science agencies (NIH, NSF, DOD), been involved in symposium organization at the local level, and have served as a mentor for junior faculty through government run workshops on grant writing. I was also awarded a Leshner Fellowship for Public Engagement by the AAAS and accordingly, have been communicating scientific discoveries to the broader community when given the opportunity, appearing on mainstream media broadcasts and in articles.

Mentorship: To date, I have mentored 12 postdoctoral researchers (2 current), 43 graduate students (11 current), and 61 undergraduates (9 current). I am currently involved in three graduate programs – Chemistry, Molecular Systems & Pharmacology, and Microbiology & Molecular Genetics and four T32 programs. In each program I am active in the recruitment and training of students throughout the year. These trainees have obtained 8 NSF graduate research fellowships and 15 honorable mentions, 3 ACS MEDI fellowship, 8 NIH T32 fellows, and 4 NIH NRSA fellowships. The average time to PhD for my graduates has been 4.5 years with an average of 7 publications/student and trainees have been placed in both academic (FIU, Cal State-Fullerton, Guam, Valdosta State, Berry, Dennison, Samford) and industry (Janssen, Minakem, GSK) positions. I have worked hard to foster a supportive lab environment. With respect to the undergraduate researchers, three have received Goldwater Foundation Scholars and eleven recognized by the NSF GRFP (6 awards, 5 HMs). At Emory I have established several programs to enhance the career development and training environment within the university to increase all career outcomes of our student's broadening interests. These have included two Chemical Biology groups, the Emory Biotech Consulting Club, and a Graduate Program Teaching Fellows program to promote undergraduate research. I am personally invested in the training of every student and tailor my mentorship to match their career aspirations.

1. Smith JR, LeBlanc AR, Wuest WM. From Natural Products to Small Molecules: Recent Advancements in Anti-MRSA Therapeutics. ACS Med Chem Lett. 2025 Apr 10;16(4):542-551. PubMed Central PMCID: PMC11995227.
2. LeBlanc AR, Wuest WM. Siderophores: A Case Study in Translational Chemical Biology. Biochemistry. 2024 Aug 6;63(15):1877-1891. PubMed Central PMCID: PMC11308372.
3. Rossiter SE, Fletcher MH, Wuest WM. Natural Products as Platforms To Overcome Antibiotic Resistance. Chem Rev. 2017 Oct 11;117(19):12415-12474. PubMed Central PMCID: PMC5869711.
4. Jennings MC, Minbiole KP, Wuest WM. Quaternary Ammonium Compounds: An Antimicrobial Mainstay and Platform for Innovation to Address Bacterial Resistance. ACS Infect Dis. 2015 Jul 10;1(7):288-303. PubMed PMID: 27622819.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2021 -	Professor, Emory University
2017 -	GRA Distinguished Investigator, Emory University
2017 - 2021	Associate Professor, Emory University
2016 - 2017	Daniel Swern Early Career Development Professor, Temple University
2015 - 2017	Scientific Founder, NovaLyse BioSolutions
2011 - 2017	Assistant Professor of Chemistry, Temple University
2008 - 2011	NRSA NIH Postdoctoral Fellow, Harvard Medical School, Christopher T. Walsh, Advisor
2003 - 2008	Graduate Research Assistant, University of Pennsylvania, Amos B. Smith, III, Advisor
2002 - 2003	Undergraduate Research Assistant, University of Notre Dame, Paul Helquist, Advisor

Honors

2025	Senior Member, National Academy of Inventors
2020	David W. Robertson Award, ACS Medicinal Chemistry
2019	Leshner Fellow, AAAS
2018	Scialog Fellow, Research Corporation
2017	ESI MIRA, National Institute of General Medical Sciences
2017	Young Investigator Award, ACS Infectious Diseases
2016	Thieme Chemistry Journal Award, Editors of Synthesis, Synlett, and Synfacts
2015	NSF CAREER AWARD, National Science Foundation
2014	Italia-Eire Foundation Distinguished Teacher of the Year, Temple University
2013	Kaufman Young Investigator Award, The Pittsburgh Foundation
2013	Young Investigator Award, Center for Biofilm Engineering, Montana State University
2013	Early Career Reviewer, National Institutes of Health
2013	Summer Research Award, Temple University
2010	NRSA Postdoctoral Fellowship, National Institutes of Health
2006	Alfred Douty Graduate Fellowship, University of Pennsylvania
2006	Excellence in Undergraduate Teaching, University of Pennsylvania
2005	President, Bayer Student Seminar Series, University of Pennsylvania
2003	Merck Award, University of Notre Dame

C. Contribution to Science

1. **Total synthesis, biological evaluation, and target identification of the *P. aeruginosa*-specific antibiotic Promysalin.** Promysalin is a Pseudomonas species-specific antibacterial and antivirulence natural product first identified in 2011. However, the initial report did not disclose the absolute or relative stereochemistry nor study the specific properties. Our group has developed the first total synthesis of the natural product in a concise, modular, and high-yielding manner (8 steps, 35% overall yield), which has led to the structural characterization and the synthesis of >100 analogs. The synthetic compound possesses potent inhibitory activity against pathogenic strains of *P. aeruginosa*; however, the compound does not affect the growth of other Pseudomonads or other bacteria. We utilized diverted total synthesis to uncover a previously unknown iron-binding capacity of promysalin and recently identified the target as succinate dehydrogenase. Further efforts elucidated that the species-selectivity is a result of differential metabolism in Pseudomonads, which we have leveraged toward developing an improved analog and using it as a tool compound to understand virulence in gram-negative bacteria.

    a. Post SJ, Keohane CE, Rossiter LM, Kaplan AR, Khowsathit J, Matuska K, Karanicolas J, Wuest WM. Target-Based Design of Promysalin Analogues Identifies a New Putative Binding Cleft in Succinate Dehydrogenase. ACS Infect Dis. 2020 Jun 12;6(6):1372-1377. PubMed Central PMCID: PMC7293565.
    b. Keohane CE, Steele AD, Fetzer C, Khowsathit J, Van Tyne D, Moynié L, Gilmore MS, Karanicolas J, Sieber SA, Wuest WM. Promysalin Elicits Species-Selective Inhibition of Pseudomonas aeruginosa by Targeting Succinate Dehydrogenase. J Am Chem Soc. 2018 Feb 7;140(5):1774-1782. PubMed Central PMCID: PMC5869686.
    c. Steele AD, Keohane CE, Knouse KW, Rossiter SE, Williams SJ, Wuest WM. Diverted Total Synthesis of Promysalin Analogs Demonstrates That an Iron-Binding Motif Is Responsible for Its Narrow-Spectrum Antibacterial Activity. J Am Chem Soc. 2016 May 11;138(18):5833-6. PubMed Central PMCID: PMC5084090.
    d. Steele AD, Knouse KW, Keohane CE, Wuest WM. Total synthesis and biological investigation of (-)-promysalin. J Am Chem Soc. 2015 Jun 17;137(23):7314-7. PubMed PMID: 26024439.

2. **Total synthesis and biological evaluation of natural products that target the oral pathogen *S. mutans*.** The development of narrow-spectrum inhibitors that specifically target pathogenic bacteria in the oral microbiome would provide a new avenue of therapy. Both Honokiol and Carolacton are natural products that were reported to specifically target *S. mutans*. Our lab, in collaboration with the Kozlowski group, was able to identify Honokiol-inspired analogs that are highly potent against oral pathogens. Concurrently, we have also had a longstanding interest in Carolacton, a compound capable of specifically killing *S. mutans* cells transitioning into a biofilm, a property that is unlike any other compound previously identified. In 2014 our group, in collaboration with Phillips and coworkers, reported the most efficient total synthesis of carolacton to date. Through diverted total synthesis we identified a simplified analog that retained carolacton-like activity, one that inhibited biofilm formation, and a third that stalled biofilm growth. Most recently, we have discovered that this class of molecules is the first inhibitor to target a bacterial hydrolase CHAP-domain.

    a. Scharnow AM, Solinski AE, Rowe S, Drechsel I, Zhang H, Shaw E, Page JE, Wu H, Sieber SA, Wuest WM. In Situ Biofilm Affinity-Based Protein Profiling Identifies the Streptococcal Hydrolase GbpB as the Target of a Carolacton-Inspired Chemical Probe. J Am Chem Soc. 2024 Aug 21;146(33):23449-23456. PubMed Central PMCID: PMC11345752.
    b. Solinski AE, Koval AB, Brzozowski RS, Morrison KR, Fraboni AJ, Carson CE, Eshraghi AR, Zhou G, Quivey RG Jr, Voelz VA, Buttaro BA, Wuest WM. Diverted Total Synthesis of Carolacton-Inspired Analogs Yields Three Distinct Phenotypes in Streptococcus mutans Biofilms. J Am Chem Soc. 2017 May 31;139(21):7188-7191. PubMed Central PMCID: PMC5891724.
    c. Solinski AE, Ochoa C, Lee YE, Paniak T, Kozlowski MC, Wuest WM. Honokiol-Inspired Analogs as Inhibitors of Oral Bacteria. ACS Infect Dis. 2018 Feb 9;4(2):118-122. PubMed Central PMCID: PMC5869685.

d. Solinski AE, Scharnow AM, Fraboni AJ, Wuest WM. Synthetic Simplification of Carolacton Enables Chemical Genetic Studies in Streptococcus mutans. ACS Infect Dis. 2019 Aug 9;5(8):1480-1486. PubMed Central PMCID: PMC7169375.

3. **Development of novel approaches to kill *A. baumannii***. *A. baumannii* is a gram-negative bacterium typically found in hospital settings and labeled as a critical threat by the CDC. Our lab has taken several approaches to develop novel treatments for this pathogen. We have identified two natural products that are active against the pathogen and work in distinct ways. In collaboration with the Sieber lab, we were able to show that xanthocillin targets heme biosynthesis and kills *A. baumannii* at low concentrations. Concurrently, we have also completed the total synthesis of the reported structure of Cahuitamycin and analogs, a potent anti-biofilm compound and are currently working on elucidating its true configuration. We have also looked to repurpose or modify existing methods to kill this pathogen. We recently demonstrated that we could repurpose the FDA-approved migraine drug, fendiline, to specifically kill carbapenem-resistant *A. baumannii* through a unique mechanism. Finally, we developed new disinfectants that are extremely potent against hospital-acquired strains serving as a potential front-line treatment against the pathogen.

   a. Hübner I, Shapiro JA, Hoßmann J, Drechsel J, Hacker SM, Rather PN, Pieper DH, Wuest WM, Sieber SA. Broad Spectrum Antibiotic Xanthocillin X Effectively Kills Acinetobacter baumannii via Dysregulation of Heme Biosynthesis. ACS Cent Sci. 2021 Mar 24;7(3):488-498. PubMed Central PMCID: PMC8006170.
   b. Shapiro JA, Post SJ, Smith GC, Wuest WM. Total Synthesis of the Reported Structure of Cahuitamycin A: Insights into an Elusive Natural Product Scaffold. Org Lett. 2023 Dec 29;25(51):9243-9248. PubMed Central PMCID: PMC10758118.
   c. Colquhoun JM, Brzezinski C, Ji A, Marotta J, Elsen JAV, Bonomo RA, May KL, Sieber SA, Grabowicz M, Wuest WM, Rather PN. Proc. Nat. Acad. Sci. 2025 Jun 17;122(24):e2423650122. PubMed Central PMCID: PMC12184509.
   d. Michaud ME, Allen RA, Morrison-Lewis KR, Sanchez CA, Minbiole KPC, Post SJ, Wuest WM. Quaternary Phosphonium Compound Unveiled as a Potent Disinfectant against Highly Resistant Acinetobacter baumannii Clinical Isolates. ACS Infect Dis. 2022 Nov 11;8(11):2307-2314. PubMed Central PMCID: PMC11995017.

4. **Repurposing of FDA-approved drugs for the development of anti-*MRSA* therapeutics.** The development of new compounds that target methicillin-resistant *S. aureus* are still greatly needed given the burden this pathogen places on hospitals. One approach to combat *MRSA* is to depolarize their membranes, an underexplored area of research. This class of compounds has the added benefit of working synergistically with existing antibiotics to potentiate activity against persister cells, which are typically present in chronic infections (specifically MRSA and VRSA). Our lab has worked in close collaboration with the Mylonakis lab, by leveraging their *C. elegans* hit to lead screen, to identify and repurpose three unique clinical candidates that were developed for other purposes (adapalene, bithionol, nTZDpa). We synthesized three unique libraries of compounds and tested their bioactivity to gain a structure-activity relationship. We are now optimizing these novel classes of antimicrobials to both improve bioactivity and limit toxicity with the goal of translating these findings to the clinic. Finally, in collaboration with the Sieber group, we have identified a small molecule, PK150, that prevents hemolysis in *S. aureus* and potently inhibits biofilm formation without affecting bacteria viability. This molecule is currently being optimized for clinical trials in Europe.

   a. Kim W, Steele AD, Zhu W, Csatary EE, Fricke N, Dekarske MM, Jayamani E, Pan W, Kwon B, Sinitsa IF, Rosen JL, Conery AL, Fuchs BB, Vlahovska PM, Ausubel FM, Gao H, Wuest WM, Mylonakis E. Discovery and Optimization of nTZDpa as an Antibiotic Effective Against Bacterial Persisters. ACS Infect Dis. 2018 Nov 9;4(11):1540-1545. PubMed Central PMCID: PMC6468991.
   b. Kim W, Zhu W, Hendricks GL, Van Tyne D, Steele AD, Keohane CE, Fricke N, Conery AL, Shen S, Pan W, Lee K, Rajamuthiah R, Fuchs BB, Vlahovska PM, Wuest WM, Gilmore MS, Gao H, Ausubel FM, Mylonakis E. A new class of synthetic retinoid antibiotics effective against bacterial persisters. Nature. 2018 Apr 5;556(7699):103-107. PubMed Central PMCID: PMC6462414.

c. Kim W, Zou G, Hari TPA, Wilt IK, Zhu W, Galle N, Faizi HA, Hendricks GL, Tori K, Pan W, Huang X, Steele AD, Csatary EE, Dekarske MM, Rosen JL, Ribeiro NQ, Lee K, Port J, Fuchs BB, Vlahovska PM, Wuest WM, Gao H, Ausubel FM, Mylonakis E. A selective membrane-targeting repurposed antibiotic with activity against persistent methicillin-resistant Staphylococcus aureus. Proc Natl Acad Sci U S A. 2019 Aug 13;116(33):16529-16534. PubMed Central PMCID: PMC6697817.

d. Le P, Kunold E, Macsics R, Rox K, Jennings MC, Ugur I, Reinecke M, Chaves-Moreno D, Hackl MW, Fetzer C, Mandl FAM, Lehmann J, Korotkov VS, Hacker SM, Kuster B, Antes I, Pieper DH, Rohde M, Wuest WM, Medina E, Sieber SA. Repurposing human kinase inhibitors to create an antibiotic active against drug-resistant Staphylococcus aureus, persisters and biofilms. Nat Chem. 2020 Feb;12(2):145-158. PubMed Central PMCID: PMC6994260.

5. **Development of next generation cationic antiseptics for hospital sanitation.** Quaternary ammonium cationic (QAC) amphiphiles are ubiquitous, with their uses ranging from household cleaners to commercial hospital biocides. Their rampant use has led to an epidemic of QAC-resistant MRSA now found in >50% of clinical isolates. These resistant strains, when found in bacterial biofilms, can persist even the most potent QAC disinfectants warranting the development of "next generation" biocides. Our group, in collaboration with the Minbiole lab, has developed >900 multiQAC scaffolds that are 10-100x more effective than conventional QACs and can eradicate mature biofilms at the lowest concentrations ever reported (50 uM). Most recently, we developed a novel class of quaternary phosphonium cationic (QPC) amphiphiles that display a previously unknown mechanism of action against gram-negative bacteria, specifically targeting their inner membrane. We have shown that this mode of action is able to overcome the intrinsic resistance of hospital-acquired *P. aeruginosa* strains that, in some cases, are completely resistant to commercial cleaners. We are currently enlisting our library of QACs and QPCs as tool compounds to better understand the nuance in their activity. In addition, we are enlisting AI/ML to propose the next generation of chemical structures with higher therapeutic indices to pursue for development. This work has resulted in over 40 publications (>30 undergraduate authors), six patents, the formation of NovaLyse BioSolutions, and exploratory licenses to four separate industrial partners.

a. Sanchez CA, Vargas-Cuebas GG, Michaud ME, Allen RA, Morrison-Lewis KR, Siddiqui S, Minbiole KPC, Wuest WM. Highly Effective Biocides against Pseudomonas aeruginosa Reveal New Mechanistic Insights Across Gram-Negative Bacteria. ACS Infect Dis. 2024 Nov 8;10(11):3868-3879. PubMed Central PMCID: PMC11555683.

b. Brayton SR, Toles ZEA, Sanchez CA, Michaud ME, Thierer LM, Keller TM, Risener CJ, Quave CL, Wuest WM, Minbiole KPC. Soft QPCs: Biscationic Quaternary Phosphonium Compounds as Soft Antimicrobial Agents. ACS Infect Dis. 2023 Apr 14;9(4):943-951. PubMed Central PMCID: PMC10111419.

c. Jennings MC, Buttaro BA, Minbiole KP, Wuest WM. Bioorganic Investigation of Multicationic Antimicrobials to Combat QAC-Resistant Staphylococcus aureus. ACS Infect Dis. 2015 Jul 10;1(7):304-9. PubMed PMID: 27622820.

d. Jennings MC, Ator LE, Paniak TJ, Minbiole KP, Wuest WM. Biofilm-eradicating properties of quaternary ammonium amphiphiles: simple mimics of antimicrobial peptides. Chembiochem. 2014 Oct 13;15(15):2211-5. PubMed PMID: 25147134.

Complete List of Published Work in My Bibliography

(Citation metrics: h-index = 43; i10-index = 90; NIH iCite – RCR = 17.1 (Max), 1.94 (Mean), 231.4 (Weighted))

https://www.ncbi.nlm.nih.gov/myncbi/1jCMszhZcigMul/bibliography/public/