BIOGRAPHICAL SKETCH

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NAME: Long, Timothy E.

eRA COMMONS USER NAME (credential, e.g., agency login): tlong1

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
University of South Florida, Tampa, FL	B.S.	08/1999	Biology
University of South Florida, Tampa, FL	Ph.D.	12/2003	Chemistry
University of Notre Dame, Notre Dame, IN	Postdoc	08/2006	Chemistry

A. Personal Statement

I am an Associate Professor of Pharmaceutical Sciences, and my research is focused on the development new therapies for antibiotic-resistant infection. I have a background in microbiology and organic chemistry, with specific training and expertise in the medicinal chemistry and antibiotic pharmacology. I am currently funded by NIH for the development of disulfiram (Antabuse™) as an antibiotic adjuvant for MRSA infections with intermediate vancomycin (VISA) resistance. The project is conducting pharmacological studies to define the mechanism of action of disulfiram as an anti-MRSA agent, pharmacokinetics of disulfiram-vancomycin combinations and the pharmacodynamics parameters using a VISA infections model. I have published original research articles and reviews in medicinal chemistry related to the design and synthesis of bioactive compounds for the treatment of infectious diseases, cancer, and neurodegenerative diseases.

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

2020/03/01 –2024/02/28
Title: Discovery of Disulfiram as an Anti-MRSA Antibiotic Adjuvant
Agency: NIH/NIAID 1R15AI151970-01 (PI: Long)
Description: The purpose of this project is determine whether repurposed disulfiram can be used as an antibiotic adjuvant for MRSA infections with reduced vancomycin susceptibility.
Role: PD/PI

Citations:

1. Chavva H, Meka Y, **Long TE**. Antimicrobial pharmacodynamics of vancomycin and disulfiram (Antabuse®) in Staphylococcus aureus. Front Microbiol. 2023 Jan 6;13:1092257. doi: 10.3389/fmicb.2022.1092257. PMID: 36687633.
2. Lewis AD, Riedel TM, Kesler MBA, Varney ME, **Long TE**. Pharmacological evaluation of disulfiram analogs as antimicrobial agents and their application as inhibitors of fosB-mediated fosfomycin resistance. J Antibiot (Tokyo). 2022 Mar;75(3):146-154. doi: 10.1038/s41429-022-00500-2. Epub 2022 Jan 20. PMID: 35058577
3. Shanholtzer CN, Rice C, Watson K, Carreon H, **Long TE**. Effect of copper on the antifungal activity of disulfiram (Antabuse®) in fluconazole-resistant Candida strains. Med Mycol. 2022 Mar 17;60(4):myac016. doi: 10.1093/mmy/myac016. PMID: 35188195

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2023	National Institutes of Health ZAI1 MMO-D (J1) Support for Research Excellence (SuRE) Award (R16 Clinical Trial Not Allowed), Ad Hoc Reviewer
2023	Department of Defense Infection Control and Prevention panel (ICM-1) Defense Medical Research and Development Program (DMRDP), Ad Hoc Reviewer
2022	National Institutes of Health ZRG1 AIDC-D (80) A - Infectious Diseases and Immunology Research Enhancement Review, Ad Hoc Reviewer
2021	National Institutes of Health ZRG1 AIDC-S (80) A - Infectious Diseases and Immunology Research Enhancement Review, Ad Hoc Reviewer
2021	National Science Foundation Phase I COVID: Drug Discovery and Delivery, Ad Hoc Reviewer
2020	National Institutes of Health ZAI1 MFH-M J1 1, Partnerships for Countermeasures Against Select Pathogens (R01 Clinical Trials Not Allowed), Ad Hoc Reviewer
2020	National Science Foundation Phase I: Pharmaceutical Technologies SBIR/STTR Grants, Ad Hoc Reviewer
2020 -	Graduate Studies Director, School of Pharmacy, Marshall University, Huntington, WV
2019-Present	Associate Professor, School of Pharmacy, Marshall University, Huntington, WV
2019	Department of Defense Peer-Reviewed Medical Research Program (PRMRP) Pre-Antimicrobial Resistance Grants, Ad Hoc Reviewer
2018	West Virginia Clinical and Translational Science Institute (CTSI) Pilot Grants, Ad Hoc Reviewer
2017	Department of Defense Peer-Reviewed Medical Research Program (PRMRP) Pre Antimicrobial Resistance Grants, Ad Hoc Reviewer
2014-Present	Adjunct Faculty Member, School of Medicine, Marshall University, Huntington, WV
2013-2019	Assistant Professor, School of Pharmacy, Marshall University, Huntington, WV
2013	Research Corporation for Science Advancement Cottrell College Science Awards, Ad Hoc Reviewer
2013	American Association of Colleges of Pharmacy (AACP) New Investigator Awards, Ad Hoc Reviewer
2006-2013	Assistant Professor, College of Pharmacy, University of Georgia, Athens, GA

Honors

2020	Dean’s Award for Research Excellence, Marshall School of Pharmacy
2018	Instructor of the Year Award, P2 Class, Marshall School of Pharmacy
2017	Instructor of the Year Award, P2 Class, Marshall School of Pharmacy
2017	Course Team of the Year Award, P2 Class, Marshall School of Pharmacy
2017	Course Team of the Year Award, P2 Class, Marshall School of Pharmacy
2013	Faculty of the Year, Phi Delta Chi Professional Pharmacy Fraternity, Alpha Iota Chapter
2012	Faculty of the Year, Phi Delta Chi Professional Pharmacy Fraternity, Alpha Iota Chapter
2002	Fred L. & Helen M. Tharp Outstanding First Year Graduate Student Award, Department of Chemistry, University of South Florida

C. Contributions to Science

1. Since 2013, my laboratory at Marshall University has been extensively involved in antibacterial drug discovery research. During this time, we have published original research articles and reviews in the area. My lab is currently investigating the use disulfiram (Antabuse™) and other disulfide drugs as adjuvants for the treatment of multidrug-resistant *S. aureus* infections. We have discovered that disulfiram reduces the MIC of vancomycin in VISA and VRSA to MIC and sub-MIC levels observed in MRSA. Mechanistic studies suggest that disulfiram and its primary metabolite disrupt energy production and cause perturbations in bacillithiol-mediated redox homeostasis.

a. Chavva H, Meka Y, **Long TE.** Antimicrobial pharmacodynamics of vancomycin and disulfiram (Antabuse®) in Staphylococcus aureus. Front Microbiol. 2023 Jan 6;13:1092257. doi: 10.3389/fmicb.2022.1092257. PMID: 36687633.
b. Lewis AD, Riedel TM, Kesler MBA, Varney ME, **Long TE**. Pharmacological evaluation of disulfiram analogs as antimicrobial agents and their application as inhibitors of fosB-mediated fosfomycin resistance. J Antibiot (Tokyo). 2022 Mar;75(3):146-154. doi: 10.1038/s41429-022-00500-2. Epub 2022 Jan 20. PMID: 35058577
c. Moore JA, Meakin M, Earl MH, Kummer TM, McAleer JP, **Long TE.** Effects of caspofungin, tolcapone and other FDA-approved medications on MRSA susceptibility to vancomycin. J Glob Antimicrob Resist. 2020;22:283-289. PMID: 32247076
d. Frazier KR, Moore JA, **Long TE**. Antibacterial activity of disulfiram and its metabolites. J Appl Microbiol. 2019;126(1):79-86. PMID: 30160334

2. Since 2014, I have collaborated with Dr. Hongwei Yu at Marshall University on projects related to the discovery of novel treatments for mucoid *Pseudomonas aeruginosa*. These include the evaluation of synthetic anionic fluoroquinolone as alginate-penetrating antibiotics and aerosolized rifaximin as an antibiotic adjuvant for the treatment of *Pseudomonas* infections in cystic fibrosis. We have also collaborated on his research related to the bioengineering of medical-grade alginate from *Pseudomonas.* I have provided expertise on the analysis of the chemical composition of *Pseudomonas* alginate by HPLC, MS, and FT-IR.

a. Kirby BD, Al Ahmar R, Withers TR, Valentine ME, Valentovic M, **Long TE**, Gaskins JR, Yu HD. Efficacy of aerosolized rifaximin versus tobramycin for treatment of *Pseudomonas aeruginosa* pneumonia in mice. Antimicrob Agents Chemother. 2019;63(7):e02341-18. PMID: 31010865.
b. Valentine ME, Kirby BD, Withers TR, Johnson SL, **Long TE**, Hao Y, Lam JS, Niles RM, Yu HD. Generation of a highly attenuated strain of *Pseudomonas aeruginosa* for commercial production of alginate. Microb Biotechnol. 2020;13(1):162-175. PMID: 31006977.
c. **Long TE,** Keding LC, Lewis DD, Anstead MI, Withers TR, Yu HD. Anionic fluoroquinolones as antibacterials against biofilm-producing *Pseudomonas aeruginosa*. Bioorg Med Chem Lett. 2016;26(4):1305-1309. PMID: 26826023.

3. As a faculty member and Ph.D. student, I have conducted research on the design and synthesis of bioactive compounds against various cancers. During my doctoral training, I synthesized antineoplastic compounds with the β-lactam ring system that were evaluated against human leukemia, breast, prostate, and head-and-neck cancers by Dr. Q. Ping Dao's lab at the H. Lee Moffitt Cancer Center & Research Institute. As a faculty member, my lab designed and synthesized novel haloenol morpholinones as anti-neoplastic agents in collaboration with Dr. Brian Cumming at the University of Georgia. Analogs derived from L- and D-phenylglycine were found to be the most effective antagonists of LNCaP and PC-3 cell growth. Mechanistic studies revealed that the inhibitors induced G2/M arrest and the (S)-enantiomer derivatives was an inhibitor of cytosolic iPLA2-beta. As a faculty member at Marshall University, I collaborated with Dr. Ruhul Amin's lab on the synthesis of cyclic dipeptides based on a natural product pharmacophore for anticancer testing against head-and-neck cancers. I also have an exciting, active collaboration with Dr. Piyalo Dasgupta lab on the synthesis and evaluation of non-pungent capsaicin (red pepper) analogs as irinotecan adjuvants for treating lung cancers.

a. Brown KC, Modi KJ, Light RS, Cox AJ, **Long TE**, Gadepalli RS, Rimoldi JM, Miles SL, Rankin G, Valentovic M, Denning KL, Tirona MT, Finch PT, Hess JA, Dasgupta P. Anticancer Activity of Region B Capsaicin Analogs. J Med Chem. 2023 Apr 13;66(7):4294-4323. PMCID: PMC10108357.
b. Adeluola AA, Bosomtwe N, **Long TE**, Amin ARMR. Context-dependent activation of p53 target genes and induction of apoptosis by actinomycin D in aerodigestive tract cancers. Apoptosis. 2022;27(5-6):342-353. PMCID: PMC9133209
c. Mock JN, Taliaferro JP, Lu X, Patel SK, Cummings BS, **Long TE**. Haloenol pyranones and morpholinones as antineoplastic agents of prostate cancer. Bioorg Med Chem Lett. 2012 Jul 15;22(14):4854-8. PubMed PMID: 22677312; PubMed Central PMCID: PMC3376906.

4. From 2009-12, my lab investigated phosphonium cations of electron-transport inhibitors as antiparasitic agent. Antagonists of protozoal co-enzyme Q were designed to have an electrostatic attraction for the negatively-charged mitochondrion in parasitic organisms. The central hypothesis is that the inhibitors will

possess enhanced therapeutic efficacy resulting from the charge-mediated accumulation of the cations in protozoal mitochondria. We further postulated that this targeted delivery approach to selectively direct antagonists into the mitochondrion will preempt parasite exposure to sublethal drug concentrations that can trigger drug-resistance via mutations of co-enzyme binding sites. In collaboration with Philip Rosenthal's lab at UCSF, our findings demonstrated that the pharmacological properties of naphthoquinone-based antimalarials can be enhanced with attachment of a phosphonium group to the molecules.

a. **Long TE**, Lu X, Galizzi M, Docampo R, Gut J, Rosenthal PJ. Phosphonium lipocations as antiparasitic agents. Bioorg Med Chem Lett. 2012;22(8):2976-2979. PMID: 22414614.
b. Lu X, Altharawi A, Hansen EN, **Long TE**. Phase-transfer catalysts in the O-alkylation of 2-hydroxynaphthoquinones. Synthesis. 2012, 44(20):3225-30.
c. Lu X, Altharawi A, Gut J, Rosenthal PJ, **Long TE**. 1,4-naphthoquinone cations as antiplasmodial agents: hydroxy-, acyloxy-, and alkoxy-substituted analogues. ACS Med Chem Lett. 2012;3(12):1029-1033. PMID: 24936235.

Complete List of Published Work in My Bibliography:

https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/48449511/?sort=date&direction=descending