



Timothy A. Wencewicz, PhD
Assistant Professor
Department of Chemistry
Washington University in St. Louis

Title: New Antibiotics from Nature's Chemical Inventory

Abstract: A contemporary approach to antibiotic drug discovery in academics will be presented as vignettes on strategies ongoing in the Wencewicz lab. Topics include checkpoint inhibitors of nitrogen metabolism (bacteriostatic agents), disruptors of iron acquisition (antivirulence agents), inhibitors of emerging resistance enzymes (adjuvant therapies), and completely novel antibacterial agents. Emphasis will be placed on the elucidation of molecular mechanisms and the use of natural products and synthetic variants as chemical probes and lead scaffolds. Despite our entry into the era of antibiotic resistance, an argument will be made that the future *is* bright for antibiotics thanks to Nature's rich chemical inventory.

Timothy A. Wencewicz, PhD – CV – January 2019

Washington University in St. Louis
Department of Chemistry
Phone: 314-935-7247
Email: wencewicz@wustl.edu
<https://pages.wustl.edu/wencewiczlab>

Laboratory Sciences Rm 401c
Campus Box 1134
One Brookings Drive
St. Louis, MO
63130

Education

September 2011 PhD, Chemistry, University of Notre Dame, South Bend, IN
May 2006 BS, Chemistry & Mathematics, Southeast Missouri State Univ., Cape Girardeau, MO

Research and Teaching Appointments

July 2013 – present Assistant Professor, Dept. of Chemistry, Washington University, St. Louis, MO
Research Focus: Bioorganic Chemistry

Sept 2011 – July 2013 Postdoctoral Research Assistant, Dept. of Biological Chemistry & Molecular
Pharmacology, Harvard Medical School, Boston, MA
Laboratory of Prof. Christopher T. Walsh (biosynthetic enzymology)

July 2006 – Sept 2011 Graduate Student, Chem & Biochem Dept., University of Notre Dame, South Bend, IN
Laboratory of Prof. Marvin J. Miller (synthetic organic chemistry)

April 2008 – July 2008 Research Intern, Dept. of Microbiology, Hans Knöll Institute, Jena, Germany
Laboratory of Dr. Ute Möllmann (evaluation of new antibiotic scaffolds)

Sept. 2004 – July 2006 Undergraduate Research, Dept. of Chemistry, Southeast Missouri State University
Laboratory of Prof. Mohammed Hashmat Ali (green oxidation chemistry)

Awards, Scholarships, and Fellowships

Washington University in St. Louis

St. Louis, MO

2018 • Sloan Research Fellowship
2017 • Cottrell Scholars Award
2017 • NSF CAREER Award
2016 • NIH Mentoring Workshop for New Faculty in Organic and Biological Chemistry
2016 • American Chemical Society Infectious Diseases Young Investigator Award
2015 • American Chemical Society Division of Biological Chemistry Travel Award
2014 • Oak Ridge Associated Universities Ralph E. Powe Junior Faculty Enhancement Award

University of Notre Dame

Notre Dame, IN

2012 • Eli J. and Helen Shaheen Graduate School Award in Science (ND's top research award)
2010 – 2011 • Rohm & Haas Outstanding Graduate Student Award (Dept's top research award)
 • Jeremiah Freeman Award for Teaching in Organic Chemistry (Dept's top teaching award)
2007 – 2010 • Chemistry-Biochemistry-Biology Interface Program Fellow (NIH T32GM075762)
2006 • KANEB Outstanding Teaching Assistant Award; Brother Columba Curran Fellowship

2006	• Provost Award for College of Science (SEMO's top research award)
2006	• Chem. Dept. Outstanding Graduating Senior Award (Dept's top research award)
2005	• Department of Chemistry Service Award (Dept's top teaching award)
2004	• ACS Polymer Education Committee Outstanding Performance in Org. Chem. Award
2004	• Undergraduate Sophomore Organic Chemistry Achievement Award
2003	• Department of Chemistry Outstanding Freshman Award
2002	• Regents Scholarship; Missouri Bright Flight Scholarship

Professional Activities

- WUSTL Division of Biology & Biomedical Sciences (DBBS) Faculty Member (2013 – present)
- WUSTL Siteman Cancer Center Faculty Member (2014 – present)
- American Chemical Society Member (2004 – present)
- American Society of Microbiology Member (2011 – present)
- American Society for Biochemistry and Molecular Biology (2017 – present)
- Society for Industrial Microbiology and Biotechnology (2014 – 2015)
- ExxonMobil Partners in Academic Laboratory Safety (PALS) Faculty Member (2013 – present)
- Curator of the Christopher T. Walsh Strain Collection (2012 – present)
- Reviewer: *Proceedings of the National Academy of Sciences*, *Journal of the American Chemical Society*, *Journal of Organic Chemistry*, *FEBS Letters*, *Bioorganic & Medicinal Chemistry*, *Journal of Medicinal Chemistry*, *ACS Medicinal Chemistry Letters*, *Cell Chemical Biology*, *Biochemistry*, *Nature Chemical Biology*, *RSC Advances*, *Chemical Science*, *ACS Chemical Biology*, *Natural Product Reports*, *ACS Infectious Diseases*, *Journal of Biological Chemistry*, *Journal of Biological Inorganic Chemistry*, *Frontiers in Microbiology*, *eLIFE*
- Grant proposal reviewer: National Science Foundation (panelist), Research Corporation for Science Advancement, North Carolina Biotechnology Center
- Member of the University of Notre Dame Graduate and Research Advisory Council (2014 – 2017)
- Spotlight Session Organizer on “Emerging Antibiotics from Nature”: 2018 ASBMB National Meeting
- **Invited seminars:** U Florida (2018), Auburn (2018), Duke (2018), ASP (2018), Biometals (2018), SERMACS (2018), ASBMB (2018), Buffalo (2018), Vanderbilt (2018), U Kentucky (2018), SIUE (2018), UIUC (2018), UCLA (2017), Emory (2017), Murray State (2017), GRC on Enzymes, Coenzymes, and Metabolic Pathways (2017), University of Wisconsin-Madison (2017, Perlman Antibiotic Symposium), Wichita State (2017), GRC on Metals in Medicine (2016), Monsanto (2016), Virginia Tech (2016), U Mississippi (2016), University of Missouri–Columbia (2016), University of Notre Dame (2016, 2013), University of Missouri–St. Louis (2015), Truman State University (2015), Christopher Newport University (2015), Southeast Missouri State University (2014), Washington University School of Medicine (2013, 2014, 2015)
- **Courses taught:** Chem262 (organic chem II), Chem451 (organic chem III), Chem453 (bioorganic chemistry)

Patent Applications

1. **Wenciewicz, T. A.**; Schaffer, J. E.; Reck, M. R. “Chemoenzymatic Synthesis of Peptide Beta-Lactones.” WU 016508-PRO1, patent application #62/471,183, filing date 03/14/2017.
2. **Wenciewicz, T. A.**; Markley, J. L.; Tolia, N.; Dantas, G.; Park, J.; Gasparrini, A.; Forsberg, K.; Vogel, J. “Inhibition and Diagnostics of Emerging Tetracycline Resistance Enzymes.” WU 016593-PRO1, patent application #15/633,254, filing date 03/18/2018.

Publications

Textbooks

1. Walsh, C. T.; **Wencewicz, T. A.** "Antibiotics: Challenges, Mechanisms, Opportunities." January **2016**, ASM Press, Washington DC, USA. ISBN 9781555819309

Book Chapters

1. **Wencewicz, T. A.***; Miller, M. J. "Sideromycins as Pathogen-Targeted Antibiotics." in *Topics in Medicinal Chemistry, 26, Antibacterials, Volume II, 2017*, edited by Fisher, J. F.; Mobashery, S.; Miller, M. J.; Springer, Berlin, Heidelberg. DOI: https://doi.org/10.1007/7355_2017_19. ISBN 978-3-319-70838-6.

Peer-Reviewed Articles in Professional Journals

Published During Time at WUSTL (undergraduate coauthors are underlined):

29. Bailey, D. C.; Bohac, T. J.; Shapiro, J. A.; Giblin, D. E.; Wencewicz, T. A.*; Gulick, A. M.* "Crystal Structure of the Siderophore Binding Protein BauB Bound to an Unusual 2:1 Complex Between Acinetobactin and Ferric Iron." *Biochemistry* **2018**, *57*, 6653–6661.
28. Markley, J. L.; Morse, T. L.; Rath, N. P.; **Wencewicz, T. A.*** "Photocyclization of Beta-Ketoformamides to 3-Hydroxy-Beta-Lactams" *Tetrahedron* **2018**, *74*, 2743-2753.
27. Markley, J. L.; **Wencewicz, T. A.*** "Tetracycline Inactivating Enzymes" *Frontiers in Microbiology*, **2018**, *9*, article 1058. DOI: <https://doi.org/10.3389/fmicb.2018.01058> invited by Dr. Graeme Conn to submit a review article for a special issue entitled "Bacterial Mechanisms of Antibiotic Resistance: A Structural Perspective".
26. Sann Rivera, G. M.; Beamish, C. R.; **Wencewicz, T. A.*** "Immobilized FhuD2 Siderophore-Binding Protein Enables Purification of Salmycin Sideromycins from *Streptomyces violaceus* DSM 8286" *ACS Infectious Diseases* **2018**, *4*, 845-859.
25. Patrick, G. J.; Fang, L.; Schaefer, J.; Singh, S.; Bowman, G. R.; **Wencewicz, T. A.*** "Mechanistic basis for ATP-dependent inhibition of glutamine synthetase by tabtoxinine- β -lactam." *Biochemistry* **2018**, *57*, 117-135. **Invited for special issue entitled "Future of Biochemistry"**.
24. Bohac, T. J.; Shapiro, J. A.; **Wencewicz, T. A.*** "Rigid oxazole acinetobactin analog blocks siderophore cycling in *Acinetobacter baumannii*." *ACS Infectious Diseases* **2017**, *3*, 802-806.
23. Schaffer, J. E.; Reck, M. R.; Prasad, N. K.; **Wencewicz, T. A.*** "Beta-Lactone formation during antibiotic cleavage from a non-ribosomal peptide synthetase." *Nature Chemical Biology* **2017**, *13*, 737-744. ***F1000 highlighted article.**
22. Park, J.; Gasparrini, A. J.; Reck, M. R.; Symister, C.; Elliott, J. L.; Vogel, J. P.; **Wencewicz, T. A.***; Dantas, G.*; Tolia, N. H.* "Plasticity, dynamics, and inhibition of emerging tetracycline-resistance enzymes." *Nature Chemical Biology* **2017**, *13*, 730-736. ***Co-corresponding authors.**
21. Shapiro, J. A.; **Wencewicz, T. A.*** "Structure-function studies of acinetobactin analogs." *Metallomics* **2017**, *9*, 463-470. **Featured on inside journal cover. Editor's choice as "HOT ARTICLE"**.
20. Endicott, N. P.; Lee, E.; **Wencewicz, T. A.*** "Structural basis for xenosiderophore utilization by the human pathogen *Staphylococcus aureus*." *ACS Infectious Diseases* **2017**, *3*, 542-553.
19. **Wencewicz, T. A.*** "New antibiotics from nature's chemical inventory." *Bioorganic & Medicinal Chemistry*, **2016**, *24*, 6227-6252. **Invited article for antibiotics special issue featuring world leaders in the field.**

18. Shapiro, J. A.; **Wencewicz, T. A.*** "Acinetobactin Isomerization Enables Adaptive Iron Acquisition in *Acinetobacter baumannii* through pH-Triggered Siderophore Swapping." *ACS Infectious Diseases* **2016**, 2, 157-168. **Featured as cover article for Feb 2016 issue.**
17. Hart, K. M.; Reck, M.; Bowman, G.; **Wencewicz, T. A.*** "Tabtoxinine- β -Lactam is a 'Stealth' β -Lactam Antibiotic that Evades β -Lactamase-Mediated Antibiotic Resistance." *Med. Chem. Commun.* **2016**, 7, 118-127. **Invited article for antibiotics special issue featuring world leaders in the field.**
16. Gelman, S. J.; Mahieu, N. G.; Cho, K.; Llufrío, E. M.; **Wencewicz, T. A.**; Patti, G. J.* "Evidence that 2-Hydroxyglutarate is Not Readily Metabolized in Colorectal Carcinoma Cells." *Cancer Metabolism* **2015**, 3:13, doi: 10.1186/s40170-015-0139-z, eCollection 2015.
15. Forsberg, K. J.; Patel, S.; **Wencewicz, T. A.***; Dantas, G.* "The Tetracycline Destructases: A Novel Family of Tetracycline-Inactivating Enzymes." *Chemistry & Biology*, **2015**, 22, 888-897. ***Co-corresponding authors.**

Published Prior to WUSTL (undergraduate coauthors are underlined):

14. Walsh, C. T.; **Wencewicz, T. A.** "Prospects for new antibiotics: A molecule-centered perspective." *J. Antibiotics* **2014**, 67, 7-22. **Winner of JA Medal for Excellence.**
13. **Wencewicz, T. A.**; Miller, M. J. "Biscatecholate-monohydroxamate mixed ligand siderophore-carbacephalosporin conjugates are selective sideromycin antibiotics that target *Acinetobacter baumannii*." *J. Med. Chem.* **2013**, 56, 4044-4052.
12. **Wencewicz, T. A.**; Long, T. E.; Möllmann, U.; Miller, M. J. "Trihydroxamate siderophore-fluoroquinolone conjugates are selective sideromycin antibiotics that target *Staphylococcus aureus*." *Bioconjugate Chemistry* **2013**, 24, 473-486.
11. **Wencewicz, T. A.**; Walsh, C. T. "*P. syringae* self protection from tabtoxinine- β -lactam by ligase TblF and acetylase Ttr." *Biochemistry* **2012**, 51, 7712-7725.
10. Walsh, C. T.; **Wencewicz, T. A.** "Flavoenzymes: Versatile catalysts in biosynthetic pathways." *Nat. Prod. Rep.* **2012**, 30, 175-200.
9. **Wencewicz, T. A.**; Oliver, A. G.; Miller, M. J. "Iron(III)-templated macrolactonization of trihydroxamate siderophores." *Org. Lett.* **2012**, 14, 4390-4393.
8. **Wencewicz, T. A.**; Yang, B.; Rudloff, J. R.; Oliver, A. G.; Miller, M. J. "N-O chemistry for antibiotics: Discovery of *N*-alkyl-*N*-(pyridin-2-yl)hydroxylamine scaffolds as selective antibacterial agents using nitroso Diels-Alder and ene chemistry." *J. Med. Chem.* **2011**, 54, 6843-6858.
7. Mayfield, J. A.; Frederick, R. E.; Streit, B. R.; **Wencewicz, T. A.**; Ballou, D. P.; DuBois, J. L. "Comprehensive spectroscopic, steady state, and transient kinetic studies of a representative siderophore-associated flavin monooxygenase." *J. Biol. Chem.* **2010**, 285, 30375-30388.
6. Yan, S.; Miller, M. J.; **Wencewicz, T. A.**; Möllmann, U. "Syntheses and biological evaluation of new cephalosporin-oxazolidinone conjugates." *Med. Chem. Comm.* **2010**, 1, 145-148.
5. Yan, S.; Miller, M. J.; **Wencewicz, T. A.**; Möllmann, U. "Syntheses and antibacterial activity studies of new oxazolidinones from nitroso Diels-Alder chemistry." *Bioorg. & Med. Chem. Lett.* **2010**, 20, 1302-1305.
4. **Wencewicz, T. A.**; Möllmann, U.; Long, T. E.; Miller, M. J. "Is drug release necessary for antimicrobial activity of siderophore-drug conjugates? Syntheses and biological studies of the naturally occurring salmycin 'Trojan Horse' antibiotics and synthetic desferridanoxamine-antibiotic conjugates." *Biomaterials* **2009**, 22, 633-648.

3. Ali, M. H.; Hedell, J.; **Wencewicz, T.** "Oxidation of sulfides to sulfoxides with 1,3-dibromo-5,5-dimethylhydantoin in the presence of hydrated silica gel." *Journal of Sulfur Chemistry* **2009**, *30*, 160-166.
2. Ali, M. H.; Kriedelbaugh, D.; **Wencewicz, T.** "Ceric ammonium nitrate (CAN) catalyzed oxidation of sulfides to sulfoxides." *Synthesis* **2007**, *22*, 3507-3511.
1. Ali, M. H.; Hartman, M.; Lamp, K.; Schmitz, C.; **Wencewicz, T.** "Oxidation of sulfides with *N*-bromosuccinimide in the presence of hydrated silica gel." *Synthetic Commun.* **2006**, *36*, 1769-1777.

Research Support

Active

1R01AI123394-01, NIH/NIAID, 02/11/16 – 01/31/21

TITLE: Structural, Mechanistic, & Evolutionary Characterization of Tetracycline Destructases

ROLE: Wencewicz (Co-PI), Tolia (Co-PI), Dantas (Co-PI)

CHE-1654611, NSF-CAREER, 06/01/17 – 05/31/22

TITLE: CAREER: Siderophore Chemistry in Pathogenic Bacteria

ROLE: PI

CS-24056, Cottrell Scholars Award, Research Corporation for Science Advancement, 07/1/17–06/30/20

TITLE: Chemoenzymatic Synthesis of Strained Beta-Lactones

ROLE: PI

Sloan Fellowship, 04/01/18–03/31/20

ROLE: PI

MI-PD-II-2018-748, Interdisciplinary Research Initiative, Children's Discovery Institute, St. Louis Children's Hospital, Washington University School of Medicine, 02/01/18 – 01/31/21

TITLE: Blocking Nitrogen Metabolism in TB

ROLE: PI

W. M. Keck Fellowship, 07/01/18–06/30/19

ROLE: PI

Completed

Oak Ridge Associated Universities Ralph E. Powe Jr Faculty Enhancement Award, 06/01/2014–05/31/2015

TITLE: Rusting Out Bacteria in the Host-Pathogen Battle for Iron

ROLE: PI

My Research in the News

Southeast Alumnus Awarded Sloan Fellowship for STEM Achievements featured in Southeast Missouri State University News Alumni Spotlights on May 17, 2018, written by Michelle Queiser: <http://news.semo.edu/southeast-alumnus-awarded-sloan-fellowship-for-stem-achievements/>

Global Antibiotic Use is Rising, Spurring More Antibiotic Resistance featured in *Mashable* on March 26, 2018, written by Mark Kaufman: <https://mashable.com/2018/03/26/antibiotics-rising-globally-resistance-superbugs/#mJPZieqywOqi>

Wencewicz Wins Sloan Fellowship: Chemist Chases Future Antibiotics Inspired by Nature featured in *theSOURCE* by Washington University in St. Louis on February 15, 2018, written by Talia Ogliore: <https://source.wustl.edu/2018/02/wencewicz-wins-sloan-fellowship/>

WashU Innovates: Tim Wencewicz video highlighting our invention describing a platform for the chemoenzymatic synthesis of peptide beta-lactones on November 7, 2017, video produced by Tom Rodgers: <https://www.youtube.com/watch?v=XuJl62GxgEQ&feature=youtu.be>

The Next Enchanted Ring?, featured in *theSOURCE* by Washington University in St. Louis on May 30, 2017, written by Diana Lutz: <https://source.wustl.edu/2017/05/next-enchanted-ring/>

Antibiotic Resistance Circumvented in Lab, featured in *theSOURCE* by Washington University in St. Louis on May 8, 2017, written by Diana Lutz: <https://source.wustl.edu/2017/05/antibiotic-resistance-circumvented-lab/>

Wencewicz Selected as 2017 Cottrell Scholar, featured in *theSOURCE* by Washington University in St. Louis on March 28, 2017, written by Diana Lutz: <https://source.wustl.edu/2017/03/wencewicz-selected-2017-cottrell-scholar/>

Research Corporation for Science Advancement Announces 2017 Cottrell Scholars, featured in Research Corporation for Science Advancement news on February 21, 2017: <http://rescorp.org/news/2017/02/research-corporation-for-science-advancement-announces-2017-cottrell-schola>

A Chemist's Quest for New Antibiotics, podcast for Hold That Thought, Washington University in St. Louis on November 9, 2016 during world antibiotic awareness week, hosted by Claire Navarro: <https://thought.artsci.wustl.edu/podcasts/antibiotic-resistance>

Odom, Wencewicz Win Young Investigator Awards for Study of Infectious Diseases, featured in *theSOURCE* by Washington University in St. Louis on September 2, 2016, written by Diana Lutz: <https://source.wustl.edu/2016/09/odom-wencewicz-win-young-investigator-awards-study-infectious-diseases/>

Alumnus Receives ACS Infectious Diseases Young Investigator Award, feature in University of Notre Dame College of Science News on August 30, 2016, written by Gene Stowe and Marissa Gebhard: <https://science.nd.edu/news/alumnus-receives-acis-infectious-diseases-young-investigator-award/>

Inaugural ACS Infectious Diseases Young Investigator Award Winners Announced, featured in ACS axial on July 22, 2016, written by Brooke Howell: <http://axial.acs.org/2016/07/22/odom-wencewicz-pires-win-inaugural-acis-infectious-diseases-young-investigator-awards/>

Washington University Planning to Usher in New Era of Scientific Discovery, featured in the St. Louis Post-Dispatch on May 23, 2016, written by Koran Addo: http://www.stltoday.com/news/local/education/washington-university-planning-to-usher-in-new-era-of-scientific/article_bc5ae845-c1cb-54f4-be27-26e634bfc6a5.html

A Kryptonite for Pathogens, featured in *The Pathologist*, April 2016, issue 18, pages 38-40 written by Timothy Wencewicz: <https://thepathologist.com/issues/0416/a-kryptonite-for-pathogens/>

Two-For-One Bacterial Virulence Factor Revealed, featured in *theSOURCE* by Washington University in St. Louis on January 15, 2016, written by Diana Lutz: <https://source.wustl.edu/2016/01/two-one-bacterial-virulence-factor-revealed/>

Slaying Bacteria With Their Own Weapons, featured in *theSOURCE* by Washington University in St. Louis on June 26, 2014, written by Diana Lutz: <https://source.wustl.edu/2014/06/slaying-bacteria-with-their-own-weapons/>

A Freezer at Washington University May Hold the Key to Developing New Antibiotics, featured on KRCU morning show, St. Louis Public Radio on June 4, 2014, hosted by Jess Jiang: <http://news.stlpublicradio.org/post/freezer-washington-university-may-hold-key-developing-new-antibiotics#stream/0>

2014 Ralph E. Powe Junior Faculty Enhancement Awards, featured in Oak Ridge Associated Universities news release on May 30, 2014, written by Pam Bonee and Wendy West: <https://www.ora.u.org/media-center/news-releases/2014/fy14-42-2014-powe-awards.aspx>

New Drugs for Bad Bugs, featured in *theSOURCE* by Washington University in St. Louis on March 5, 2014, written by Diana Lutz: <https://source.wustl.edu/2014/03/new-drugs-for-bad-bugs/>