BIOGRAPHICAL SKETCH

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NAME: Wipf, Peter

eRA COMMONS USER NAME:

POSITION TITLE: Distinguished University Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Univ. of Zürich, Zürich, Switzerland	Dipl. Chem.	07/1984	Chemistry & Biochem.
Univ. of Zürich, Zürich, Switzerland	PhD	07/1987	Chemistry
Univ. of Virginia, Charlottesville, VA	Postdoc	08/1990	Organic Chemistry

A. Personal Statement.

I have the specific training, expertise, and proven track record in medicinal chemistry, structure-based drug design, and complex natural and unnatural product synthesis to design, synthesize and evaluate small molecule therapeutics. I have led an independent research group since 1990, and published >500 peer-reviewed papers and patents. My group has pursued medicinal chemistry projects since 1995, and one of our compounds, PX-866, moved on to several Phase II clinical trials for the treatment of cancer. Since 2002, I am the Director of the Center for Chemical Methodologies and Library Development (UPCMLD), and the co-leader of the University of Pittsburgh Chemical Diversity Center (UPCDC), a Participant in NCI's Chemical Biology Consortium. Since 2012, I am also a co-leader of the Cancer Therapeutics Program at the University of Pittsburgh Cancer Institute. I was one of two founding members of the University of Pittsburgh Drug Discovery Institute (UP-DDI) in 2004. This track record, as well as my results from other ongoing and past programs, clearly demonstrate my commitment to interdisciplinary biomedical research, as well as my ability to interact with a diverse set of colleagues in biology, chemistry, pharmacology, and medicine. We remain committed to the search for innovative cures harnessing the power of small molecules. In summary, I have a demonstrated record of developing and deploying the tools of synthetic and medicinal chemistry to investigate important hypotheses in the biological and health-related sciences.

B. Positions

1990-1995 Assistant Professor, Department of Chemistry, University of Pittsburgh, Pittsburgh, PA
1995-1997 Associate Professor, Department of Chemistry, University of Pittsburgh, Pittsburgh, PA
1997-2004 Professor, Department of Chemistry, University of Pittsburgh, Pittsburgh, PA
2001- Professor, Department of Pharmaceutical Sciences, University of Pittsburgh, Pittsburgh, PA
2002- Adjunct Professor, Department of Chemistry, Duke University, Durham, NC
2002- Director, Center for Chemical Methodologies & Library Development, University of Pittsburgh
2004- Distinguished University Professor, University of Pittsburgh, Pittsburgh, PA
2004- Deputy Director, then Associate Director (since 2012), Drug Discovery Institute, Pittsburgh, PA
2012- Co-Leader, UPCI Molecular Therapeutics and Drug Discovery Program, Pittsburgh, PA.
2014- Professor, Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA

Selected Honors

1993-1995 Eli Lilly Grantee
1994-1996 Alfred P. Sloan Research Fellow
1994-1999 NSF Presidential Faculty Fellow
1995 Zeneca Award for Excellence in Chemistry

1995 Merck Young Investigator Award
1995 Camille Dreyfus Teacher-Scholar Award
1998 Arthur C. Cope Scholar Award
2002 Fellow of the American Association for the Advancement of Science (AAAS)
2003 International Society for Heterocyclic Chemistry (ISHC) Katritzky Award
2004 Fellow of the Royal Society of Chemistry (FRSC)
2008 Chancellor's Distinguished Research Award
2009 ACS Guenther Award in the Chemistry of Natural Products
2010 Fellow of the American Chemical Society (ACS)
2012 ACS Pittsburgh Award
2013 Edward W. Morley Award
2013 Harry and Carol Mosher Award of the Santa Clara Valley Section of the ACS
2014-2017 Humboldt Research Award of the Alexander von Humboldt Foundation
2015 Provost's Award for Excellence in Mentoring

Selected Other Experience and Professional Memberships

1998-2003 NIH Medicinal Chemistry Study Section, Member, and Chair
2002-2006 Organic & Biomolecular Chemistry, Associate Editor for North America
2002-2010 Organic Syntheses, Inc., Board of Editors
2007- Organic Reactions, Inc., Board of Directors
2009- ACS Medicinal Chemistry Letters, Associate Editor
2015-2018 Chair-Elect, Chair, and Retiring Chair of the Section on Pharmaceutical Sciences of the AAAS

C. Contribution to Science

1. *Medicinal Chemistry and Drug Discovery.* In 2004, we published a seminal, collaborative study of the antitumor activity of PX-866, a mechanism-based phosphoinositide-3-kinase (PI-3K) inhibitor. This paper has been cited 244 times, and PX-866, designed and first synthesized in our lab, has completed multiple Phase 1 and 2 trials in several tumor indications. Most significantly, PX-866 is the only irreversible inhibitor among a group of ca. 35 PI-3K targeting compounds in clinical trials, and it is the only one developed in an academic lab. While interest in the development of irreversible anticancer agents has recently surged, in 2004 this approach was highly iconoclastic, thus highlighting the innovative character of our drug design strategies. A second major breakthrough in our medicinal chemistry research was accomplished with the design and development of XJB-5-131. This mitochondrial-targeted agent has shown exceptional protective effects in rodent models of traumatic brain injury and Huntington's Disease, and we are committed to its further clinical development in neurodegenerative disorders.
    a. Ihle, N. T.; Williams, R.; Chow, S.; Chew, W.; Berggren, M. I.; Paine-Murrieta, G.; Minion, D. J.; Halter, R. J.; Wipf, P.; Abraham, R.; Kirkpatrick, L.; Powis, G., "Molecular pharmacology and antitumor activity of PX-866, a novel inhibitor of phosphoinositide-3-kinase signaling." *Mol. Cancer Ther.* **2004**, *3*, 763-772.
    b. Wipf, P.; Xiao, J.; Jiang, J.; Belikova, N. A.; Tyurin, V. A.; Fink, M. P.; Kagan, V. E., "Mitochondrial Targeting of Selective Electron Scavengers: Synthesis and Biological Analysis of Hemigramicidin-TEMPO Conjugates." *J. Am. Chem. Soc.* **2005**, *127*, 12460-12461.
    c. Ji, J.; Kline, A. E.; Amoscato, A.; Arias, A. S.; Sparvero, L. J.; Tyurin, V. A.; Tyrina, Y. Y.; Fink, B.; Cheng, J. P.; Alexander, H.; Clark, R. S. B.; Kochanek, P. M.; Wipf, P.; Kagan, V. E.; Bayir, H., "Global Lipidomics Identifies Cardiolipin Oxidation as a Mitochondrial Target for Redox Therapy of Acute Brain Injury." *Nat. Neurosci.* **2012**, *15*(10), 1407-1413. PMCID: PMC3697869.
    d. Xun, Z.; Rivera-Sanchez, S.; Ayala-Penã, S.; Lim, J.; Budworth, H.; Skoda, E. M.; Robbins, P. D.; Niedernhofer, L. J.; Wipf, P.; McMurray, C. T., "Targeting of XJB-5-131 to Mitochondria Suppresses Oxidative DNA Damage and Motor Decline in a Mouse Model of Huntington's Disease." *Cell Rep.* **2012**, *2*(5), 1137-1142. PMCID: PMC3513647.

2. *Natural Products Total Synthesis.* We have completed more than 30 total syntheses of complex natural products. With westiellamide, lissoclinamide 7, cyclotheonamide A, and trunkamide A, my group investigated highly modified cyclopeptide alkaloids that inspired new synthetic strategies. We are also widely recognized for applying arene oxidation strategies for key strategic conversions in total syntheses of naphthalenediol spiroketal natural products, including nisamycin, diepoxin σ, and preussomerin CP_1. A

lynchpin of our unified synthetic approach toward Stemona alkaloids is the use of a bicyclic oxidation product of tyrosine. This scaffold has been employed by our group for total syntheses of the natural products aranorosin, stenine, and aeruginosin. In the first total synthesis of the pentacyclic alkaloid tuberostemonine, a single stereocenter of the amino acid precursor was relayed into 9 of the 10 stereogenic carbons of the target molecule. Cycloaddition processes continue to expand the efficiency of organic synthesis and the structural diversity of the known small molecule universe. Our intramolecular Diels-Alder reaction of β-hydroxy 2-amino-furans delivers substituted indoles in a convergent approach. In addition to the IMDAF reaction, a second noteworthy feature in our synthesis of the ergot alkaloid cycloclavine is a stereoselective intramolecular methylene cyclopropane Diels-Alder reaction.

a. Wipf, P.; Fritch, P. C., "Total Synthesis and Assignment of Configuration of Lissoclinamide 7." *J. Am. Chem. Soc.* **1996**, *118*, 12358-67.
b. Wipf, P.; Jung, J.-K., "Formal Total Synthesis of (+)-Diepoxin σ." *J. Org. Chem.* **2000**, *65*, 6319-6337.
c. Wipf, P.; Rector, S. R., "Asymmetric Total Syntheses of Tuberostemonine, Didehydrotuberostemonine and 13-Epituberostemonine." *J. Am. Chem. Soc.* **2005**, *127*, 225-235.
d. Petronijevic, F. R.; Wipf, P., "Total Synthesis of (±)-Cycloclavine and (±)-5-*epi*-Cycloclavine." *J. Am. Chem. Soc.* **2011**, *133*(20), 7704-7707. PMCID: PMC3111057.

3. *Synthetic Methods.* Our methods just for the preparation of 5-membered heterocycles have been cited >4,000 times, including >700 citations for our three most cited papers on oxazole/oxazoline synthesis. Many industrial laboratories have been using ourazole and dihydropyrimidine methods for pharmaceutical SAR and API syntheses, thus clearly illustrating the benefits to society. Starting with transmetalation reactions of organocuprates and zirconocenes, we have also greatly expanded the scope of organozirconium chemistry over the past 20 years. Our group reported the first asymmetric protocol for the addition of alkenyl zirconocenes to aldehydes as well as several innovative cascade reactions with imines. For example, the multicomponent reaction of alkenyl zirconocene, alkynyl imine and zinc carbenoid in the presence of dimethylzinc leads to novel *C*,*C*-dicyclopropylmethylamines. The formation of intermediate bicyclo[1.1.0]butanes represents the first synthetically useful example of a double C,C-σ-bond insertion, and the increase in structural complexity from reactant to products is highlighted by the formation of nine new C,C-bonds in the final product. A related noteworthy contribution to organometallic chemistry is the discovery of the water effect in the asymmetric zirconocene-catalyzed alkylalumination of alkenes. He and his group originally discovered the rate-acceleration of water in the carboalumination of alkynes, and this modification of Negishi's process has since become a standard experimental protocol.
    a. Wipf, P.; Lim, S., "Rapid Carboalumination of Alkynes in the Presence of Water." *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1068-1070.
    b. Wipf, P.; Ribe, S., "Water/MAO Acceleration of the Zirconocene-Catalyzed Asymmetric Methylalumination of α-Olefins." *Org. Lett.* **2000**, *2*, 1713-1716.
    c. Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R., "Synthesis of Functionalized Oxazolines and Oxazoles with DAST and Deoxo-Fluor." *Org. Lett.* **2000**, *2*, 1165-1168.
    d. Walczak, M. A. A.; Wipf, P., "Rhodium(I)-Catalyzed Cycloisomerizations of Bicyclobutanes." *J. Am. Chem. Soc.* **2008**, *130*(22), 6924-6925. PMCID: PMC2754197.

4. *Computational Methods.* Since 1997, our group has been interested in the computational prediction of macroscopic properties, specifically ORD, CD, RAO and NMR as well as chemical diversity computations, to complement our natural products and medicinal chemistry studies. In interdisciplinary collaborations, we are exploring the computational assignment as well as the combined computational-chiroptical elucidation of the relative and absolute stereochemistry of organic molecules. After our initial benchmark success with hennoxazole A, we have expanded this approach to several other natural products and new synthetic organic compounds with unassigned absolute configurations. We are also investigating novel approaches to structural diversity by elucidating the small molecule universe.
    a. Kondru, R. K.; Wipf, P.; Beratan, D. N., "Theory Assisted Determination of Absolute Stereochemistry for Complex Natural Products via Computation of Molar Rotation Angles." *J. Am. Chem. Soc.* **1998**, *120*, 2204-2208.
    b. Kondru, R. K.; Wipf, P.; Beratan, D. N., "Atomic Contributions to the Optical Rotation Angle as a Quantitative Probe of Molecular Chirality." *Science* **1998**, *282*, 2247-2250.
    c. Zuber, G.; Goldsmith, M.-R.; Hopkins, T. D.; Beratan, D. N.; Wipf, P., "Systematic Assignment of

the Configuration of Flexible Natural Products by Spectroscopic & Computational Methods: The Bistramide C Analysis." *Org. Lett.* **2005**, *7* (23), 5269-5272.

d. Virshup, A. M.; Contreras-García, J.; Wipf, P.; Yang, W.; Beratan, D. N., "Stochastic Voyages into Uncharted Chemical Space Produce a Representative Library of All Possible Drug-like Compounds." *J. Am. Chem. Soc.* **2013**, *135*, 7296-7303. PMCID: PMC3670418.

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