BIOGRAPHICAL SKETCH

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NAME: **Wacker, Daniel**

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

POSITION TITLE: **Assistant Professor of Pharmacological Sciences, Neuroscience**

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Munich, Munich, Germany	BSc	2003-2007	Chemistry
University of Munich, Munich, Germany	MSc	2007-2009	Biochemistry
Rockefeller University, New York, NY	Technician	2008-2009	Cell Biology
The Scripps Research Institute, La Jolla, CA	PhD	2009-2013	Biophysics
University of North Carolina, Chapel Hill, NC	Postdoc	2014-2018	Pharmacology

A. Personal Statement

The long-term goal of my laboratory at the Icahn School of Medicine is a comprehensive mechanistic understanding of important drug targets involved in a variety of pathologies using structural and pharmacological methods. We are further leveraging these insights in structure-based drug discovery towards the treatment of neuropsychiatric disorders. We are particularly interested in the structure and function of membrane receptors and transporters, and aim to design novel, target selective compounds that help delineate the role of these proteins in mental illnesses, addiction, learning and cognitive disorders, as well as other pathologies.

Much of my previous work has focused on crystallographic and pharmacological studies of GPCRs, the largest class of drug targets in the human genome. These studies aimed at elucidating how GPCRs are activated and inhibited by a variety of therapeutic and illicit drugs. Among others, I solved crystal structures of serotonin, dopamine, and opioid receptors. During my postdoctoral training in a pharmacology and drug discovery lab, I built a GPCR crystallography program from scratch. This involved purchasing and setting up instrumentation, as well as training and leading a team of several Postdocs. Under my leadership, we determined many pharmacologically important crystal structures. Most notably, I determined the long sought-after structure of an LSD-bound serotonin receptor, the antipsychotic-bound D2 Dopamine receptor, as well as the active state of the Kappa opioid receptor. I further solved the high-resolution crystal structure of the D4 Dopamine receptor, and with my long term collaborators developed chemically novel, receptor selective high affinity agonists, with biased signaling properties at this receptor. Under my guidance, two Postdocs have since published first author publications in Science, Nature, and Cell, and started their own labs.

I have since built on these successes in my lab at Mount Sinai, where we have begun investigating the structure and function of understudied membrane drug targets, including several receptors and transporters. In an effort to develop novel therapeutic avenues for treating a variety of pathologies, we are using cutting-edge technologies including membrane protein crystallization and cryo-electron microscopy, quantitative pharmacology, and computational drug design.

B. Positions and Honors

Positions

07/2018 – Present	Associate Director, Mount Sinai Center for Therapeutics Discovery
02/2018 – Present	Assistant Professor, Department of Pharmacological Sciences, Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York (NY), USA
01/2014 – 01/2018	Postdoctoral Associate: Structural and functional characterization of G protein-coupled receptor signaling. University of North Carolina, Chapel Hill (NC), USA, Prof. Bryan Roth
07/2009 – 12/2013	Ph.D. and Postdoctoral Research: Structural basis of hallucinogen signaling through serotonin and opioid receptors. The Scripps Research Institute, La Jolla (CA), USA, Prof. Raymond Stevens
03/2008 – 07/2009	Master's Thesis: Structural and functional analysis of yeast Nup133 of the nuclear pore complex. Rockefeller University, New York (NY), USA, Prof. Günter Blobel
08/2006 – 12/2007	Undergraduate Research: Electron-microscopic single particle reconstruction of ribosome complexes. Gene Center Munich, Germany, Prof. Roland Beckmann

Honors

2016	Keystone Symposia Future of Science Fund scholarship for Keystone Symposia
2016	UNC Department of Pharmacology Retreat Best Oral Presentation Award
2010-2012	Boehringer Ingelheim Fonds PhD Fellowship
2008	MSc Graduation with distinction – among top 10% in class
2008	DAAD Foreign Exchange Research Fellowship

C. Contributions to Science

1. I have made major contributions towards a structural understanding of G Protein Coupled Receptor (GPCR) function. I contributed to the structural elucidation of numerous therapeutically important GPCRs, including the first crystal structures of the kappa opioid receptor, the glucagon receptor, the D2 and D4 dopamine receptors, and the 5-HT serotonin receptor 5-HT_{2B}, 5-HT_{2C}, and 5-HT_{1B}.

   a. ***[#]**__**Wacker D**__, [#]Wang S, [#]McCorvy JD, Betz RM, Venkatakrishnan AJ, Levit A, Lansu K, Schools Z, Che T, Nichols DE, Shoichet BK, *Dror RO, *Roth BL. Crystal structure of an LSD-bound human serotonin receptor | **Cell** 168, 377-389, (2017) - COVER

   b. __**Wacker D**__, Wang C, Katritch V, Han GW, Huang XP, Vardy E, McCorvy JD, Jiang Y, Chu M, Siu FY, Liu W, Xu HE, Cherezov V, *Roth BL, *Stevens RC. Structural Features for Functional Selectivity at Serotonin Receptors | **Science** 340, 615-619, (2013)

   c. *Wang S, Che T, Levit A, Shoichet BK, ***__Wacker D__**, *Roth BL. Structure of the D2 dopamine receptor bound to the atypical antipsychotic drug risperidone | **Nature** 555, 269-273, (2018)

   d. *[#]Wang S, ***[#]__Wacker D__**, [#]Levit A, Che T, Betz RM, McCorvy JD, Venkatakrishnan AJ, Huang XP, Dror RO, *Shoichet BK, *Roth BL. D4 dopamine receptor high-resolution structures enable the discovery of selective agonists | **Science** 358, 381-386, (2017)

   *[#]co-first authors, *co-corresponding authors*

2. Through combining structural studies with quantitative pharmacological studies, I have contributed to resolving several of the underlying molecular principles that govern how ligands modulate GPCR activity to engage differential signaling pathways. This phenomenon termed functional selectivity or biased signaling can be exploited to design drugs that specifically activate therapeutic over pathological pathways, thereby drastically reducing on-target side effects.

   a. **Wacker D**, Wang C, Katritch V, Han GW, Huang XP, Vardy E, McCorvy JD, Jiang Y, Chu M, Siu FY, Liu W, Xu HE, Cherezov V, *Roth BL, *Stevens RC. Structural Features for Functional Selectivity at Serotonin Receptors | **Science** 340, 615-619, (2013)

   b. ***#Wacker D**, #Wang S, #McCorvy JD, Betz RM, Venkatakrishnan AJ, Levit A, Lansu K, Schools Z, Che T, Nichols DE, Shoichet BK, *Dror RO, *Roth BL. Crystal structure of an LSD-bound human serotonin receptor | **Cell** 168, 377-389, (2017)

   c. Che T, Majumdar S, Zaidi SA, Kormos C, McCorvy JD, Wang S, Mosier PD, Uprety R, Vardy E, Krumm BE, Han GW, Lee MY, Pardon E, Steyaert J, Huang XP, Strachan RT, Tribo AR, Pasternak GW, Carroll IF, Stevens RC, Cherezov V, Katritch V, ***Wacker D**, *Roth BL. Structure of a nanobody-stabilized active state of the kappa opioid receptor | **Cell** 172, 55-67, (2018)

   d. **Wacker D**, Stevens RC, *Roth BL. How ligands illuminate GPCR molecular pharmacology | **Cell** 170, 414-427, (2017)

   *#co-first authors, *co-corresponding authors*

3. I have also made major contributions to structure-based drug discovery efforts providing GPCR structures for virtual ligand screening campaigns, and identifying and characterizing novel chemical matter for challenging target receptors such as the D4 dopamine receptor. I also determined the first crystal structure of a GPCR ligand developed by structure-based methods, which substantially contributed to the validation and optimization of virtual ligand screening efforts towards novel GPCR compounds.

   a. *#McCorvy JD**, #Wacker D**, #Wang S, Agegnehu B, Liu J, Lansu K, Tribo AR, Olsen RHJ, Che T, Jin J, *Roth BL. Structural determinants of 5-HT2B receptor activation and biased agonism | **Nat Struct Mol Biol** 25, 787-796 (2018)

   b. *#Wang S, ***#Wacker D**, #Levit A, Che T, Betz RM, McCorvy JD, Venkatakrishnan AJ, Huang XP, Dror RO, *Shoichet BK, *Roth BL. D4 dopamine receptor high-resolution structures enable the discovery of selective agonists | **Science** 358, 381-386, (2017)

   c. **Wacker, D.**, Stevens, R.C., *Roth, B.L. How ligands illuminate GPCR molecular pharmacology. **Cell** 170, 414-427, (2017)

   d. **#Wacker D**, #Fenalti G, #Brown MA, Katritch V, Abagyan R, Cherezov V, *Stevens RC. Conserved binding mode of human β2 adrenergic receptor inverse agonists and antagonist revealed by X-ray crystallography | **J Am Chem Soc** 132, 11443-11445, (2010)

   *#co-first authors, *co-corresponding authors*

4. In addition to small molecule compounds, antibodies are becoming increasingly useful probes to study GPCR pharmacology. I used both conventional IgG derived antigen-binding fragments (Fabs) and camelid single-chain antibodies, termed nanobodies, to structurally elucidate GPCR activation mechanisms based on distinct antibody-stabilized GPCR conformations.

   a. Che T, Majumdar S, Zaidi SA, Kormos C, McCorvy JD, Wang S, Mosier PD, Uprety R, Vardy E, Krumm BE, Han GW, Lee MY, Pardon E, Steyaert J, Huang XP, Strachan RT, Tribo AR, Pasternak GW, Carroll IF, Stevens RC, Cherezov V, Katritch V, ***Wacker D**, *Roth BL. Structure of a nanobody-stabilized active state of the kappa opioid receptor | **Cell** 172, 55-67, (2018)

b. Ishchenko A, **Wacker D**, Kapoor M, Zhang A, Han GW, Basu S, Patel N, Messerschmidt M, Weierstall U, Liu W, Katritch V, Roth BL, Stevens RC, *Cherezov V. Structural insights into the extracellular recognition of the human serotonin 2B receptor by an antibody | **Proc Natl Acad Sci USA** 114, 8223-8228, (2017)

c. English JG, Olsen RHJ, Lansu K, Patel M, White K, Cockrell AS, Singh D, Strachan RT, **Wacker D**, Roth BL. VEGAS as a Platform for Facile Directed Evolution in Mammalian Cells | **Cell** 178, 748-761, (2019)

**co-corresponding authors*

5. I participated in a larger multi-institutional collaboration with the goal to implement x-ray free-electron laser (XFEL) technology in membrane protein structural biology using crystals generated in lipidic cubic phase. This technology promises to revolutionize structural biology through enabling femtosecond timescale resolved studies, providing high quality data virtually devoid of radiation damage, and requiring minimal crystal optimization.

   a. Liu W, **Wacker D**, Gati C, Han GW, James D, Wang D, Nelson G, Weierstall U, Katritch V, Barty A, Zatsepin NA, Li D, Messerschmidt M, Boutet S, Williams GJ, Koglin JE, Seibert MM, Wang C, Shah STA, Basu S, Fromme R, Kupitz C, Rendek KN, Grotjohann I, Fromme P, Kirian RA, Beyerlein KR, White TA, Chapman HN, Caffrey M, Spence JCH, Stevens RC, *Cherezov V. Serial femtosecond crystallography of G protein-coupled receptors in lipidic cubic phase | **Science** 342, 1521-1524, (2013)

   b. Liu W, **Wacker D**, Wang D, Abola E, *Cherezov V. Femtosecond crystallography of membrane proteins in the lipidic cubic phase | **Phil Trans R So B** 369, (2014)

   c. *Weierstall U, James D, Wang C, White TA, Wang D, Liu W, Spence JC, Bruce Doak R, Nelson G, Fromme P, Fromme R, Grotjohann I, Kupitz C, Zatsepin NA, Liu H, Basu S, **Wacker D**, Han GW, Katritch V, Boutet S, Messerschmidt M, Williams GJ, Koglin JE, Marvin Seibert M, Klinker M, Gati C, Shoeman RL, Barty A, Chapman HN, Kirian RA, Beyerlein KR, Stevens RC, Li D, Shah ST, Howe N, Caffrey M, *Cherezov V. Lipidic cubic phase injector facilitates membrane protein serial femtosecond crystallography | **Nat Commun** 5, 3309, (2014)

   **co-corresponding authors*

List of published work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/wacker.daniel.1/bibliography/54351448/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R35 GM133504 (PI: Wacker) 08/01/19 – 04/30/24
NIH/NIGMS
Structural Studies and Drug Discovery Illuminate Serotonin Pharmacology
Using cryo-EM and x-ray crystallography, we investigate molecular mechanisms of serotonin transporters and receptors, and leverage our insights in computational structure-based ligand discovery.

Sloan Research Fellow in Neuroscience (PI: Wacker) 09/15/19 - 09/14/21
Alfred P. Sloan Foundation
Structural Studies of the Serotonergic System Template Drug Discovery
We investigate fundamental mechanisms of serotonin signaling, transport, and modulation using a combination of x-ray crystallography, cryo-EM, ligand binding, and in vitro signaling and transport assays.

Edward Mallinckrodt, Jr. Foundation Grant (PI: Wacker) 10/01/19 - 09/30/22
Edward Mallinckrodt, Jr. Foundation
Elucidating the Molecular Mechanisms of Methadone and Fentanyl to Combat the Opioid Epidemic
Elucidation of how Fentanyl and Methadone signal through the human mu opioid receptor, using a combination of structural and pharmacological techniques

McKnight Scholar Award (PI: Wacker) 07/01/20 – 06/30/23
The McKnight Endowment Fund for Neuroscience
Accelerating Drug Discovery for Cognitive Disorders through Structural Studies of a Serotonin Receptor
We study the structure and function of the 5-HT7 receptor, a key mediator of the pro-cognitive effects of several antipsychotic, and will discover novel tool compounds to delineate the receptors role in cognition

Completed Research Support

Friedman Brain Institute Research Scholarship (PI: Wacker, Filizola) 01/01/19 - 12/31/19
Friedman Brain Institute
Empowering Structure-Based Discovery of New Medicines to Combat the Opioid Epidemic
Elucidation of how clinically used opioids modulate the activity of the human mu opioid receptor, using a combination of structural, computational, and pharmacological techniques