BIOGRAPHICAL SKETCH

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NAME: Roth, Bryan L.

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

POSITION TITLE: Michael Hooker Distinguished Professor of Pharmacology

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
Carroll College, Helena MT	BA	06/77	Biology and Chemistry
St. Louis University Medical School, St. Louis, MO	MD, PhD	06/83	Medicine and Biochemistry
NIMH Lab of Preclinical Pharmacology, Washington, DC	Guest Worker/Post-Doctoral	07/83-06/88	Pharmacology
Stanford University Medical Center	Psychiatry Residency	07/88-06/91	Psychiatry
Nancy Pritzker Laboratory, Stanford University	Fellowship	06/89-06/91	Molecular Biology

A. Personal Statement: I believe my lab has made important discoveries and invented useful technologies in the general areas of molecular pharmacology, GPCR structure and function and synthetic neurobiology. I believe many would consider me to have specific expertise in *in vitro* and *in vivo* molecular pharmacology, synthetic and chemical biology and GPCR structural biology. I have published >500 papers, my work is highly cited and could be considered by a few individuals to have some impact (**h-index =153**; >100,000 citations via Google Scholar). I am listed as an inventor on >40 published/submitted US, WO and foreign patents. My lab also has solved many dozens of GPCR structures via cryo-EM and crystallography of which ~100 are currently published in the Protein Data Bank. I have also openly shared reagents generated by my lab with **ADDGENE shipping >120,000 plasmids from my lab as of April 2025.**

In terms of recent publications**, since 2009 my lab has published 8 papers in Science, 14 papers in Cell and >20 papers in Nature**.

I was elected to the National Academy of Medicine (formerly IOM) in 2014, was named a 'Highly Cited Scientist' by Thompson Reuters in 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023 and 2024 and one of the 'World's Most Influential Scientific Minds' in 2015 by Thompson Reuters. I was elected to the American Academy of Arts and Sciences in 2019.

Major discoveries my lab made include:

a. The molecular target for the widely abused hallucinogen salvinorin A (Roth et al, ***PNAS*** 2002)—a finding which greatly accelerated studies which described the structure of its molecular target—the κ-opioid receptor (Wu et al ***Nature*** 2012; Che et al, ***Cell*** 2018) and the importance of the sodium site on the δ-opioid (Fenalti, Giguere et al, ***Nature*** 2014) and dopamine (Wang et al, **Science** 2017; Wang et al, **Nature** 2018) receptor structure and function.

b. The molecular target responsible for the valvulopathic side-effects of the notorious appetite suppression drug fenfluramine (Rothman et al, ***Circulation*** 2000)—a finding which also led to the discovery of other approved medications with this life-threatening side-effect (Roth ***NEJM*** 2007) and the structural determination of serotonin receptors (Wacker et al, ***Science***, 2013). Recently my lab solved the structures of psychedelics and other drugs in complex with human serotonin receptors (Wacker et al, **Cell** 2017; Kim et al, **Cell** 2020; Gumpper et al, **Cell Report** 2022; Zheng et al, **Nature Struct Mo Bio** 2022; Cao et al, **Neuron** 2022)

c. The 'hidden' pharmacology of approved drugs (Roth et al ***Nature Rev Drug Discov*** 2004; Keiser et al, ***Nature*** 2009) which has led to a novel cheminformatics approach to design multi-target ligands *de novo* (Besnard et al, ***Nature*** 2012). This led, for instance to the identification of topoisomerase inhibitors as potential therapeutic agents for Angelman's Syndrome (Huang et al, ***Nature*** 2012) and to the discovery of novel allosteric modulators for orphan and pharmacologically 'dark' GPCRs (Huang et al, ***Nature*** 2015) along with the structures of orphan GPCRs with tool compounds (Cao et al, **Nature** 2021; Liu et al **Nature Chem Bio** 2022). Relevant to this application we solved the structure of Tas2R14 (Kim et al, **Nature** 2024)

Ongoing projects I wish to highlight include:

RO1DA055656 Roth and Shoichet (MPI) 2022-2027
Structure and function of MRG family receptors

RO1MH112205 Roth and Shoichet (MPI) 2021-2026
Molecular details of psychoactive drug actions.

R37DA045657 Roth (PI) 2018-2028 (MERIT Award)
Mechanistic insights into LSD actions at 5-HT2A serotonin receptors

NIMH Psychoactive Drug Screening Program Roth (PI) (2024-2029)

U19NS138975-01 (Scherrer Contact PI; Roth Co-I) 2024-2029
Developing small molecules to engage an analgesic GPCR in pain unpleasantness neural circuits

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2016-present. Co-founder of Epiodyne Pharmaceuticals
2022-2024 Co-founder of Onsero Pharmaceuticals
2021-present. Scientific Advisory Boards: Septerna, Escient, Epiodyne, ImprintBio, Lassogen
2020-2024. Executive Editor Biochemistry
2007-present. Appointment as the Michael Hooker Distinguished Professor of Protein Therapeutics and Translational Proteomics, UNC School of Medicine.
2006-present Professor of Pharmacology, University of North Carolina Chapel Hill Medical School with Joint Appointment in Chemical Biology and Medicinal Chemistry and Director in Program in Translational Proteomics, UNC-Chapel Hill.
2003-2006 Professor of Biochemistry Case Western Reserve University School of Medicine with secondary appointments in Psychiatry, Oncology and Neurosciences
2001 Change of Tenure to Department of Biochemistry, Case Western Reserve University School of Medicine
2000 Award of Tenure, Department of Psychiatry, Case Western Reserve University
1992-2001 Associate Professor, Department of Psychiatry, Case Western Reserve University School of Medicine
1991-1992 Assistant Professor, Department of Psychiatry, Case Western Reserve University School of Medicine
1988-1991 Fellow, Nancy Pritzker Laboratory of Molecular and Developmental Neurobiology Stanford University (Roland Ciaranello)
1984-1988 Principal Investigator, Naval Medical Research Institute, Bethesda, MD (Fulfillment of military obligation)
1983-1986 Guest Worker, NIMH-Laboratory of Preclinical Pharmacology (Erminio Costa)

1977-1983 Graduate Research Assistant, St. Louis University Department of Biochemistry

Other Professional Activities:

Editorial Boards: Journal of Biological Chemistry (2001-2006); Molecular Pharmacology (2006-); Journal of Pharmacology and Experimental Therapeutics (1998-); Medicinal Chemistry Research (1996-2010); Journal of Neurochemistry/Handling Editor (2000-2007); Associate Editor Pharmacology and Therapeutics (2000-2006); Psychopharmacology (1998-); Neuropsychopharmacology (1999-2002; 2009-2012); Journal of Receptors and Signal Transduction Research (2002-2010); Associate Editor Journal of Pharmacology and Experimental Therapeutics (2005-2011); Guest Editor PNAS (2009); Faculty of 1000 Biology (2010-present); Deputy Editor Journal of Clinical Investigation (2014-2017); American Journal of Psychiatry (2019-); Executive Editor, Biochemistry (2020-2024)

National and International Service: HHMI New Investigator Reviewer (2024); National Advisory Mental Health Council (NAMHC) 2021-2024**;** Brain Initiative Working Group (2020-2024); Scientific Advisor, NIH Neurotherapeutics Blueprint Initiative (2011-2014); Scientific Advisor Molecular Libraries Screening Center Networks (2006-2009); NIMH Treatment Units for Neurocognition in Schizophrenia (TURNS)-SOU Member (2004-2009); NIMH Methods to Improve Cognition in Schizophrenia (MATRIX) Consultant; International Brain Research Organization (IBRO) Program Committee (2005); National Alliance for Research in Schizophrenia and Depression (NARSAD) Scientific Advisory Board 2004- present; Regular Member, American College of Neuropsychopharmacology (ACNP) 2004-2013; Society for Neurosciences Program Committee (1995-1998); **Regular member of NIH Study Sections** (Neuropharmacology/Neurochemistry 1996-1997; MCDN#5 1998-2005; MNPS 2006-2009); **Chairman:** Molecular Libraries Screening Centers Review Committee (MLSCN) 2004; **Chairman:** Molecular Libraries HTS Assay Review Group (2005-2007; 2010); **College of CSR Reviewers** (2010-2012). Large number of ad hoc, special study section and Board of Scientific Councilors (NIMH, NINDS) reviews.

Honors and Awards:

- National Academy of Medicine; 2014-present
- American Academy of Arts and Sciences; 2019-present
- Westheimer Medal Prize and Lecture (2024; Harvard University, Department of Chemistry)
- *Presidential Special Lecture,* Society for Neurosciences 2018
- IUPHAR Analytical Pharmacology Lecture 2018
- NIH MERIT Award (2018-2028; NIDA)
- Goodman and Gilman Award in Receptor Pharmacology–ASPET 2016
- Chemistry and Pharmacology of Drug Abuse Award, 2019 (Society for Chemistry and Pharmacology of Drug Abuse)
- Thompson Reuters Highly Cited Scientist 2016, 2017, 2018, 2020, 2021, 2022, 2023, 2024 (Pharmacology)
- Thompson Reuters Highly Cited Scientist 2015, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024 (Biology and Biochemistry)
- Thompson Reuters 'World's Most Influential Scientific Minds' 2015 (Top 1% of citations)
- PhRMA Foundation Excellence in Pharmacology Award 2011
- NARSAD Distinguished Investigator Award 2008
- Michael Hooker Distinguished Professor, UNC Chapel Hill 2007-present
- Heffter Research Institute Award for Outstanding Basic Science Research, 1999
- Past named Lectures and other awards: **Nobel Forum (Nobel Prize Foundation; 2024)**; Westehimer Medal (Harvard University, Chemistry 2024); Jack Cooper Memorial Lecture (2024; Yale); Barondes Lecture (2023; UCSF); John Daly Lecture (2023; NIDDK); Flexner Lecture (2022; UPENN); Jack Green Lecture (2021; Mt. Sinai School of Medicine); Keynote Lecture, Cannabinoid Gordon Research Conference (2021), Aghajanian Lecture (2021; Yale), Ruth K. Broad Seminar (2021; Duke); Narahashi Lecture (2020; Northwestern University); CR Stephen Lecture (2020; Washington University); Schooler Lecture (Baylor, 2019); Elaine Sanders-Bush Lecture (2019; Vanderbilt); TK Lecture International Cannabinoid Research Society (2019; Washington DC); Erminio Costa Memorial Lecture (2019; UIC); Harlen Wood Lecture (2018; Case Western Reserve University Medical School); Robert E Olsen Lecture (2018; St. Louis); Inaugural Elliot Saul Vesell Visiting Professorship (Penn State, Hershey Medical School; 2017); Sigma-Aldrich Lecture (2017; St. Louis, MO); Martin Rodbell Memorial Lecture (2107;

NIEHS, NIH, RTP); Hugh Arthur Pritchard Memorial Lecture 2016 (U Maryland); Strongwater Endowed Lecture 2016 (Rutgers); Koppanyi Lecture 2015 (Georgetown); Louis T. Goodman Lecture 2015 (OHSU); Philip S. Portoghese Lecture 2015 (Univ Minnesota); Hyman Niznik Memorial Lecture 2014 (GPCR meeting); Swammerdam Lecture 2014; Special Lecturer Society for Neurosciences Annual Meeting 2013; Irving Page Lecture 2010; Lowenthal Lecture 2010; SG Fergusson Memorial Lecture 2006; Chauncy Leake Memorial Lecturer 2005; NARSAD Independent Investigator 1998-2000; Sandoz Investigator (NARSAD) 1993-1994; NARSAD Young Investigator 1992-1994; Dana Foundation Fellowship in Neurosciences (Stanford University) 1989-1991; Phi Beta Kappa 1983

C. Contributions to Science

1. My lab has made major contributions towards understanding the structure and function of GPCRs starting with work begun in the late 1980's when I was a fellow at Stanford. Historically I have focused on the structure and function of serotonin and opioid receptors although we have studied many others (dopamine, smoothened, adrenergic, various orphan GPCRs). Additionally, my lab has also contributed to understanding serotonin receptor functional selectivity/biased signaling. I list a few of the most recent and visible contributions.

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

    b. Che, T, Majumdar S, Zaidi, SA, Ondachi P, McCovry JD, Wang S, Mosier PD, Uprety R, Vardy E, Krumm BE, Han GW, Lee M-Y, Pardon E, Steyaert J, Huang X-P, Strachan RT, Tribo AR, Pasternak GW, Carroll FI, Stevens RC, Cherezov V, Katritch V, Wacker D and Roth BL: Structure of a nanobody-stabilized active state of the kappa opioid receptor. **Cell** 172: 1-13, 2018.

    c. Wang, S, Wacker D, Levit A, Che T, Betz RM, McCorvy JD, Venkatakrishnan AJ, Huang X-P, Dror RO, Shoichet BK and Roth BL. D4 dopamine receptor high resolution structures template the discovery of selective agonists. **Science** 358: 381-386, 2017.

    d. Wang S, Che T, Levit A, Shoichet BK, Wacker D and Roth BL: Structure of the D2 dopamine receptor bound to the atypical antipsychotic drug risperidone. **Nature** 555: 269-273, 2018.

2. My lab pioneered novel cell-based screening platforms to discover chemical probes and tools for G protein coupled receptors. We have used these platforms alone and in collaboration with many labs and I list some of the more recent high-impact findings to illustrate our capability.

    a. English JG. Olsen, RHJ, Lansu K, Patel M, White K, Cockrell AS, Sing D, Strachan RT, Wacker D and Roth BL. VEGAS as a platform for facile directed evolution in mammalian cells. **Cell** 178: 748-761, 2019.

    b. Keiser M, Setola V, Irwin J, Laggner C, Abbas A, Hufesein S, Jensen N, Kuijer M, Matos R, Tran TB, Whaley R, Glennon RA, Hert J, Thomas KLH, Edwards DD, Shoichet BK* and Roth BL*. Predicting new molecular targets for known drugs. **Nature** 462: 175-181, 2009. PMID: 19881490

    **BLR and BKS=Co-Corresponding Authors*

    c. Huang X-P, Karpiak J, Kroeze WK, Zhu H, Chen X, Moy SS, Saddoris KA, Nikolova V, Farrell MS, Wang S, Mangano TJ, Deshpande DA, Jiang A, Penn RB, Jin J, Koller BH, Kenakin T, Shoichet BK* and Roth BL*. Allosteric ligands for the pharmacologically dark receptors GPR68 and GPR65. **Nature** 527: 477-48, 2015. PMID: 26704965
    **BKS and BLR co-corresponding authors*

d. Kim, K, Che T, Panova O, DiBerto JF, Lyu J, Krumm BE, Wacker D, Robertson MJ, Seven AB, Nichols DE, Shoichet BK, Skiniotis G and Roth BL. Structure of a hallucinogen activated Gq-coupled 5-HT2A serotonin receptor. **Cell** 2020.

3. My lab has pioneered large-scale **chemical genetic** approaches to discover, characterize and validate novel molecular targets for therapeutic drug discovery. These have led to many important discoveries only a few of which are listed below.
    a. Cao, C., Kang, H.J., Singh, I…. Shoichet, BK*, Fay J*, and Roth BL*. Structure, function and pharmacology of human itch GPCRs. **Nature** (2021).
    **BLR, JF and BKS co-corresponding authors*
    b. Fenalti G, Giguere PM, Katrich V, Huang X-P, Thompson AA, Cherezov V, *Roth BL and *Stevens RC: Molecular control of δ-opioid signaling. **Nature** 506: 191-196, 2014. PMID: 24413399.
    **BLR and RCS=co-corresponding authors*
    c. Manglik A, Lin H, Aryal DK, McCorv JD, DEngler D, Corder G, Levit A, Kling RC, Bernat V, Hubner H, Huang X-P, Sassano MF, Giguere PM, Lober S, Duan D, Scherrer G, *Kobilka BK, *Gmeiner P, *Roth BL, *Shoichet BK. Structure based discovery of biased μ-opioid receptor analgesics with reduced side effects. **Nature** 537: 185-195 2016. PMID: 27533032
    **BKK, PG,BLR and BKS Co-corresponding authors*.
    d. Lyu J, Wang S, Balius TE, Singh I, Levit A, Moroz YS, O'Meara MJ, Che T, Algaa E, Tomlachova K, Tomachev AA, Shoichet BK*, Roth BL* and Irwin JJ*. Ultra-large library docking for discovering new chemotypes. **Nature** 566: 224-229, 2019. PMID: 30728502
    **BKK, BLR and JJI Co-corresponding authors*.

4. My lab invented the ***chemogenetic platform*** called **DREADD** (Designer Receptors Exclusively Activated by Designer Drugs) in 2005 and published our first full paper on this technology in 2007. My lab was the first to use DREADDs to both silence and activate neurons. We have freely shared this technology with >1000 labs around the world. DREADD technology is now routinely to interrogate circuits responsible for simple and complex behaviors.
    a. BN Armbruster, X Li, S Herlitzer, M Pausch and BL Roth: Evolving the lock to fit the key to create a family of GPCRs potently activated by an inert ligand. **Proc Natl Acad Sci** 2007 Mar 20;104(12):5163-8 (**Highlighted on Cover**) PMID: 17350345
    b. GM Alexander, AC Rogan, AI Abbas, BN Armbruster, Y Pei, JA Allen, RJ Nonneman, J Hartmann, SS Moy, MA Nicolelis, JO McNamara and BL Roth: Remote control of neuronal activity in transgenic mice expressing evolved G protein coupled receptors. **Neuron** Jul 16;63(1):27-39, 2009. PMID: 19607790
    c. E Vardy, JE Robinson, C Li, RHJ Olsen, JF DiBerto, FM Sassano, X-P Huang, H Zhu, DJ Urban, JE Rittiner, NA Crowley, KE Pleil, PD Mosier, J Song, TL Kash, CJ Malanga, MJ Krashes and BL Roth: A new DREADD facilitates the multiplexed chemogenetic interrogation of behavior, **Neuron**, 86: 936-946 2015 (**Cover**). PMID: 25937170
    d. Shicheng Zhang, Ryan H Gumpper, Xi-Ping Huang, Yongfeng Liu, Brian E Krumm, Can Cao, Jonathan F Fay, Bryan L Roth: Molecular basis for selective activation of DREADD-based chemogenetics. **Nature** 612: 354-362, 2022. PMID: 36450989