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 expertise in *in vitro* and *in vivo* molecular pharmacology, synthetic and chemical biology and GPCR structural biology. I have published >420 papers, my work is highly cited and could be considered to have some impact (**h-index =107**; >45,000 citations via "Publish or Perish"®; to date >40 of my papers have been highlighted by Faculty of 1000). I am listed as an inventor on 40 published or submitted US, WO and foreign patents.

In terms of recent publications**, since 2009 my lab has published 4 papers in Science, 6 papers in Cell and 10 papers in Nature--of which 7 were Full Articles**. Additionally, I co-authored the Nature highlight of the 2012 Nobel Prize for GPCRs.

Our studies on GPCR structure and function were highlighted by **Science Signaling** as one of the 'Signaling Breakthroughs of '2014' (http://stke.sciencemag.org/content/8/358/eg1.full) and 2016 (http://stke.sciencemag.org/content/10/460/eaam5681.full) DREADD technology was highlighted by the NIMH Director as one of the 'Top 10 Advances of 2014' (http://www.nimh.nih.gov/about/director/2014/best-of-2014.shtml) and as one of the important advances in the past 10 years in Chemical Biology (http://www.nature.com/nchembio/journal/v11/n7/full/nchembio.1845.html). Other chemical biology discoveries have been highlighted by NIMH as one of the 'Top 10 Research Advances of 2011' (http://www.nimh.nih.gov/about/director/2011/nimhs-top-10-research-advances-of-2011.shtml) and by Wired Magazine as one of the 'Top 10 Scientific Breakthroughs of 2009' (http://www.wired.com/2009/12/discoveries-gallery/all/).

I was elected to the National Academy of Medicine of the National Academies of Sciences (formerly IOM) in 2014, was named a 'Highly Cited Scientist' by Thompson Reuters in 2015, 2016 and 2017 and one of the 'Worlds Most Influential Scientific Minds' in 2015 by Thompson Reuters.

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) 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 structure of LSD in complex with a human serotonin receptor (Wacker et al, **Cell** 2017).
- **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).

B. Positions and Honors:

Positions and Employment

1977-1983 Graduate Research Assistant, St. Louis University Department of Biochemistry
1983-1986 Guest Worker, NIMH-Laboratory of Preclinical Pharmacology (Erminio Costa)
1984-1988 Principal Investigator, Naval Medical Research Institute, Bethesda, MD (Fulfillment of military obligation)
1988-1991 Fellow, Nancy Pritzker Laboratory of Molecular and Developmental Neurobiology Stanford University (Roland Ciaranello)
1991-1992 Assistant Professor, Department of Psychiatry, Case Western Reserve University School of Medicine
1992-2001 Associate Professor, Department of Psychiatry, Case Western Reserve University School of Medicine
2000 Award of Tenure, Department of Psychiatry, Case Western Reserve University
2001 Change of Tenure to Department of Biochemistry, Case Western Reserve University School of Medicine
2003-2006 Professor of Biochemistry Case Western Reserve University School of Medicine with secondary appointments in Psychiatry, Oncology and Neurosciences
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.
2007-present. Appointment as the Michael Hooker Distinguished Professor of Protein Therapeutics and Translational Proteomics, UNC School of Medicine.

Other Experience and Professional Activities:

Editorial Boards: Journal of Biological Chemistry (2001-2006); Molecular Pharmacology (2006-); Journal of Pharmacology and Experimental Therapeutics (1998-); Medicinal Chemistry Research (1996-); 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).

National and International Service: 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 of the National Academies of Science; 2014-present
- *Presidential Special Lecture,* Society for Neurosciences 2018 (scheduled)
- Goodman and Gilman Award in Receptor Pharmacology–ASPET 2016
- Thompson Reuters Highly Cited Scientist 2016, 2017 (Pharmacology)
- Thompson Reuters Highly Cited Scientist 2015, 2017 (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 1999 Award for Outstanding Basic Science Research
- Past named Lectures and other awards: 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;
- Future confirmed named lectures and awards: IUPHAR Analytical Pharmacology Lecture (2018; IUPHAR Kyoto); Harlen Wood Lecture (2018; Case Western Reserve University Medical School). Presidential Special Lecture, SFN (2018).

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. NIHMS 839215 (PMID: 28129538) (**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. 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*

    b. Besnard J, Ruda GF, Setola V, Abecassis K, Rodriguez RM, Huang X-P, Norval S, Sassano MF, Shin AI, Webster LA, Simeons FRC, Stojanovski L, Prat A, Seidah NG, Constam DB, Bickerton GR, Read KD, Wetsel WC, Gilbert IH, Roth BL* and Hopkins AL*. Automated design of ligands with polypharmacology profiles. **Nature** 492: 215-220, 2012. PMID: 23235874

       **BLR and ALH=Co-Corresponding Authors*

    c. Kroeze WK, Huang X-P, Sassano F, Skiaky N, Lansu K and Roth BL: PRESTO-tango as an open source resource for interrogation of the human druggable GPCR-ome. **Nature Structural and Molecular Biology**, 22: 362-369, 2015. PMID: 25805059

    d. 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*

3. 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 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 (**Highighted 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. Dong S, Rogan SC, Roth BL: Directed molecular evolution of DREADDs. **Nature Protocols** 5(3):561-73, 2010. PMID: 20203671
    d. 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

4. 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. ***I've listed mainly collaborative efforts to indicate the collaborative nature of my lab and the NIMH Psychoactive Drug Screening Program which I have directed since 1998.***
    a. Huang HS, Allen JA, Mabb AM, King IF, Miriyala J, Taylor-Blake B, Sciaky N, Dutton JW JR. Lee HM, Chen X, Jin J, Bridges AS, *Zylka MJ, *Roth BL and *Philpot BD. Topoisomerase inhibitors unsilece the dormant allele of Ube3a in neurons. **Nature** 481: 185-199, 2011. PMID: 22190039
       **MJZ, BLR and BDP=co-corresponding authors*

b. Kim Y, Lee HM, Xiong Y, Sciaky N, Hulbert SW, Cao X, Everitt JI, Jin J, *Roth BL and *Jiang YH: Targeting the histone methyltransferase G9a activates imprinted genes and improves survival in a mouse model of Prade-Willi syndrome. **Nature Medicine** epub 26 Dec 2016. PMID: 28024084
**BLR and YHJ=co-corresponding authors*
c. 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*
d. 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*.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1dclsDheByeQ6/bibliograpahy/44893413/public/?sort=date&direction=ascending