BIOGRAPHICAL SKETCH

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NAME: Leslie B. Vosshall Ph.D.

eRA COMMONS USER NAME: LESLIEVOSSHALL

POSITION TITLE: Robin Chemers Neustein Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Columbia University	A.B.	06/1987	Biochemistry
The Rockefeller University	Ph.D.	06/1993	Molecular Genetics
Columbia University	Postdoc	09/1997	Molecular Neurobiology

A. Personal Statement

I am a molecular neurobiologist with 35 years of experience as a biomedical researcher and have directed an independent laboratory for 17 years. The main scientific focus of my laboratory is to understand the genetic basis of behavior, with particular emphasis on how organisms perceive and respond to external sensory stimuli, and how these responses are modulated by the internal physiological state of the animal. Our early work concerned olfactory perception, and we discovered two large families of insect chemosensory receptors (ORs and IRs) that are structurally and functionally distinct from those in vertebrates. We have described general principles of the function and expression of insect chemosensory receptors, and the connectivity of the sensory neurons that express them to primary processing centers in the brain. We also investigate the molecular mechanisms underlying a diverse array of stereotyped innate behaviors – including the host-seeking behavior of mosquitoes, feeding and courtship behaviors of *Drosophila*, and the genetics and psychophysics of human smell perception. In recent years, the lab has shifted its focus to founding the field of mosquito neurogenetics. The goal of this work is understand the biology that drives these insects to hunt humans and to be extremely effective vectors of infectious disease. Our group was the first to use genome editing to generate mutant mosquitoes, and we have used genetic approaches to understand the sensory cues that these animals use to detect human hosts. I have a successful history of launching trainees into biomedical careers and have created a scientific environment that fosters creativity and high-risk/high-reward research.

B. Positions and Honors

Positions and Employment

1994	Instructor, Neurobiology Course, Marine Biological Laboratory, Woods Hole, MA
1997-2000	Associate Research Scientist, Center for Neurobiology and Behavior, Howard Hughes Medical Institute, Columbia University, New York, NY. In the laboratory of Dr. Richard Axel
2000-2003	Annenberg Assistant Professor and Head of the Laboratory of Neurogenetics and Behavior, The Rockefeller University, New York, NY
2003-2006	Chemers Family Assistant Professor and Head of the Laboratory of Neurogenetics and Behavior, The Rockefeller University, New York, NY
2005-2007	Faculty, Neural Systems and Behavior Course, Marine Biological Laboratory, Woods Hole, MA
2006-2010	Chemers Family Associate Professor and Head of the Laboratory of Neurogenetics and Behavior, The Rockefeller University, New York, NY
2008-	Investigator, Howard Hughes Medical Institute
2010-	Robin Chemers Neustein Professor, and Head of the Laboratory of Neurogenetics and Behavior, The Rockefeller University, New York, NY

Other Experience and Memberships

2002-	NIH CSR review panels (NIDCD ZDC1 SRB-S, NIDCD ZDC1 SRY-Y, NIDCD CDRC, NIH/CSR SCS, NIH SCS CBSS)
2005-2016	Associate Editor, The FASEB Journal
2005-	Current Biology Editorial Board
2007-	Chemical Senses Editorial Board
2007-2012	Associate Editor, Journal of Neuroscience
2007-2014	External Review Committee Member, Max Planck Institute of Chemical Ecology
2008-2009	NINDS Basic Module Advisory Panel
2008-2015	McKnight Scholar Award Selection Committee
2008-2015	Program Committee of the Alfred P. Sloan Research Fellowships in Neuroscience
2008-	Jury Member for the Vilcek Prize for Creative Promise
2010-2014	Board of Scientific Counselors, NIH, NIDCR
2011-	Scientific Advisory Board, Institute of Molecular Pathology, Vienna, Austria
2012-	PLoS Biology Editorial Board
2013-	BioRxiv Advisory Board
2013-	Simons Foundation Quanta Magazine Advisory Board
2015-	Science Advances Editorial Board
2017	Jury Member for the Pearl Meister Greengard Award

Honors

1987	John Jay Scholar, Columbia College of Columbia University
2001	Beckman Young Investigator
2001	National Science Foundation CAREER Award
2001	McKnight Scholar
2002	John Merck Fund Award
2002	Presidential Early Career Award for Scientists and Engineers (PECASE)
2005	Rockefeller University Teaching Award
2005	New York City Mayor's Young Investigator Award for Excellence in Science and Technology
2007	Blavatnik Award for Young Scientists from the New York Academy of Sciences
2008	The International Society of Chemical Ecology Silverstein-Simeone Lecture Award
2009	Lawrence C. Katz Prize, Duke University
2010	Dart/NYU Biotechnology Alumnae Achievement Award
2011	Gill Center Young Investigator Award
2014	AAAS Fellow Election
2015	Election to the National Academy of Sciences

C. Contributions to Science

1. Although the chemosensory receptors that detect the vast number of odorants that animals can perceive were initially described in 1991 by Linda Buck and Richard Axel, the corresponding genes in the insect were unknown when I started my postdoctoral training in the Axel Lab. My early work led to the discovery of two large multi-gene families that encode insect chemosensory receptors for odorants, pheromones, and carbon dioxide. The insect odorant receptors (ORs) are atypical seven transmembrane domain proteins with no homology to odorant receptors in vertebrates. My group provided the first experimental evidence that ORs adopt an inverted topology relative to G protein-coupled receptors, that the active odorant receptor is a multimeric complex of a ligand-selective OR subunit and a co-receptor called Orco, and that they function as odor-gated non-selective cation channels. We showed that two members of the distantly related GR gene family cooperate to form a membrane receptor for carbon dioxide, an important sensory cue for insects. We identified a second gene family, the ionotropic receptors (IRs), that is related to ionotropic glutamate receptors. We showed that several of these receptors are tuned to volatile amines and acids, cues of particular relevance to vector mosquitoes. This work, begun by me as a postdoctoral fellow with Richard Axel, and continued in my own group from 2000-2008, has spawned a large field with many laboratories investigating olfactory function in a diverse group of insects. The work has practical and medical importance because it provides a means to control olfactory-guided behaviors that attract agricultural pests to food crops and disease vector insects to human hosts.

a. Larsson MC, AI Domingos, WD Jones, ME Chiappe, H Amrein, and **LB Vosshall**. 2004. *Or83b* encodes a broadly expressed odorant receptor essential for *Drosophila* olfaction. Neuron 43:703-714 PMID: 15339651
b. Benton R, S Sachse, SW Michnick, and **LB Vosshall**. 2006. Atypical membrane topology and heteromeric function of *Drosophila* odorant receptors *in vivo*. PLoS Biol 4:e20 PMID: 16402857
c. Sato, K., M Pellegrino, T Nakagawa, T Nakagawa, **LB Vosshall**, and K Touhara. 2008. Insect olfactory receptors are heteromeric ligand-gated ion channels. Nature 452:1002-1006 PMID: 18408712
d. Benton, R, KS Vannice, C Gomez-Diaz, and **LB Vosshall**. 2009. Variant ionotropic glutamate receptors as chemosensory receptors in *Drosophila*. Cell 136:149-162PMID: 19135896

2. Following my discovery of the insect ORs, I initiated a research program to discover how olfactory information is represented in the fly brain. Together with my trainees, I generated a complete set of genetic reagents that permitted us to map the projections of each class of OR-expressing sensory neurons to their targets in the early olfactory area of the brain. We discovered that each class of neurons innervates a specific glomerulus in either the larval or adult antennal lobe. This hard-wired circuit can be modulated by odor exposure, and this plasticity causes long-term changes in both the anatomy and function of olfactory circuits. By carrying out behavioral genetic experiments in the anatomically simple *Drosophila* larva, we identified populations of sensory neurons that respond to different concentrations of the same odor ligand. These neurons function in combinations to encode the perception of changing concentrations of odorants in the environment. The genetic strains produced in this phase of my career have been extremely influential and are used in dozens of laboratories worldwide to study the development, function, and plasticity of neural circuits. Because the anatomical organization of the fly olfactory system strongly resembles that of vertebrates, our work enabled new discoveries in circuit function in all animals.

a. **Vosshall LB**, AM Wong, and R Axel. 2000. An olfactory sensory map in the fly brain. Cell 96:725-736 PMID: 10943836
b. Fishilevich E, and **LB Vosshall**. 2005. Genetic and functional subdivision of the *Drosophila* antennal lobe. Curr Biol 15:1548-1553 PMID: 16139209
c. Sachse, S, Rueckert, E, Keller, A, Okada, R, Tanaka, NK, Ito, K and **LB Vosshall**. 2007. Activity-dependent plasticity in an olfactory circuit. Neuron 56:838-850 PMID: 18054860
d. Asahina, K, M Louis, S Piccinotti, and **LB Vosshall**. 2009. A circuit supporting concentration-invariant odor perception in *Drosophila*. J Biol 8:9 PMID: 19171076

3. Parallel to my insect olfaction program, I have been studying the basic rules of the human sense of smell since 2002. Together with my collaborator Andreas Keller, I carried out psychophysical experiments to debunk a controversial theory of olfaction that posited that molecular vibrations of odor molecules are sense by human ORs. We established the Rockefeller University Smell Study, which has screened the sense of smell more than 1700 human subjects. We have used this dataset to investigate some of the most central questions in olfaction: what are the interindividual differences in the human sense of smell? How many olfactory stimuli can humans discriminate? How does the chemical structure of an odorant relate to its perceived odor? Working with Hiro Matsunami's group, we discovered the first genetic basis of a specific anosmia. Humans carrying loss-of-function polymorphisms in a single OR that detects sex steroid-derived odorants show dramatically reduced sensitivity and altered perception of these smells. To test the capacity of humans to discriminate olfactory stimuli, we carried out psychophysical testing that asked subjects to distinguish complex odor mixtures with increasing component overlap. From the results, we estimated that humans can discriminate a very large number of olfactory stimuli. This work is important because the sense of smell is poorly understood relative to vision and hearing. Our work has the potential to aid in detection of smell disorders in humans.

a. Keller, A and **LB Vosshall**. 2004. A psychophysical test of the vibration theory of olfaction. Nat Neurosci 7:337-338 PMID: 15034588
b. Keller A*, H Zhuang*, Q Chi, **LB Vosshall**, and H Matsunami. *equal contribution. 2007. Genetic variation in a human odorant receptor alters odour perception. Nature 449:468-472 PMID: 17873857

c. Bushdid, C, MO Magnasco, **LB Vosshall**, and A Keller. 2014. Humans can discriminate more than 1 trillion olfactory stimuli. Science 343:1370-1372 PMID: 24653035
d. Keller A, Gerkin RC, Guan Y, Dhurandhar A, Turu G, Szalai B, Mainland JD, Ihara Y, Yu CW, Wolfinger R, Vens C, Schietgat L, De Grave K, Norel R; DREAM Olfaction Prediction Consortium., Stolovitzky G, Cecchi GA, **Vosshall LB**, Meyer P. 2017. Predicting human olfactory perception from chemical features of odor molecules. Science 355:820-826 PMID: 28219971

4. Innate behaviors such as courtship and feeding are encoded in hard-wired circuits that are subject to modulation. We have been studying these behaviors in the fly, *Drosophila melanogaster*. We developed high-throughput screening techniques in live animals to screen FDA-approved drugs for their ability to modulate feeding behavior in *Drosophila* larvae. At this life stage, these animals eat continuously, making them a possible experimental model for binge-eating disorder. This work identified potent antagonists of serotonin receptors as anti-feedants, and showed that the 5HT2 serotonin receptor is the sole target of this drug. We went on to discover a new taste circuit in adult flies that permits direct detection of ingested food in the pharynx and relays information on the quantity and quality of the meal to the brain, where this is integrated with information on hunger state to regulate ingestion. In the area of courtship behavior, we identified circuits that govern copulation behavior and female receptivity. These behaviors are critical for animals to time their courtship and sexual behavior according to external conditions and their internal physiological state. We discovered a compact circuit that monitors external dangers and weighs them against the temporal progress of effective fertilization to time copulation behavior. This work points to the existence of an internal timing mechanism that operates on a scale of minutes, an important phenomenon that has been little-studied in biology.

   a. Gasque G, Conway W, Huang J, Rao Y, and **LB Vosshall**. 2013. Small molecule drug screening in *Drosophila* identifies the 5HT2A receptor as a feeding modulation target. Sci Rep 3:srep02120 PMID: 23817146
   b. Crickmore MJ and **LB Vosshall**. 2013. Opposing dopaminergic and GABAergic neurons control the duration and persistence of copulation in *Drosophila*. Cell 155:881-893 PMID: 24209625
   c. Bussell JJ, N Yapici, SX Zhang, BJ Dickson, and **LB Vosshall**. 2014. Abdominal-B neurons control *Drosophila* virgin female receptivity. Curr Biol 24:1584-1595 PMID: 24998527
   d. Yapici, N, R Cohn, C Schusterreiter, V Ruta, **LB Vosshall**. 2016. A taste circuit from pharynx to brain that regulates ingestion by integrating food and hunger signals. Cell 165:715-729 PMID: 27040496

5. In 2008, I initiated a mosquito genetics research program that aims to dissect the genes and circuits that drive female mosquitoes to seek out human hosts. We were among the first groups to apply genome-engineering techniques to generate mutant mosquitoes. Using zinc-finger nucleases, we generated mutant mosquitoes that lack the olfactory co-receptor Orco, and found that these mosquitoes lose the ability to discriminate human from non-human hosts. Moreover, they no longer avoid the insect repellent DEET. We went on to generate mosquitoes genetically unable to detect the important chemosensory cue carbon dioxide. These animals show defects in detecting unrelated sensory cues, indicating the multiple sensory cues synergize to drive mosquito behavior. Field collections of sub-species of *Aedes aegypti* with different host preferences led to the discovery that evolutionary changes in an odorant receptor are correlated with human preference. We have developed powerful techniques to edit the genome of this vector insect using CRISPR-Cas9. This work opens up the possibility to study a wide variety of sensory pathways in this insect, as well as probing the central brain circuits that govern attraction to humans. The health relevance of this work is that mosquitoes transmit deadly infectious diseases to humans both domestically in the US and internationally. Understanding the rules by which these animals target human hosts will enable us to devise tools to reduce their capacity to spread disease.

   a. DeGennaro M, CS McBride, L Seeholzer, T Nakagawa, EJ Dennis, C Goldman, N Jasinskiene, AA James, and **LB Vosshall**. 2013. *orco* mutant mosquitoes lose strong preference for humans and are not repelled by volatile DEET. Nature 498:487-491 PMID: 23719379
   b. McMeniman CJ, RA Corfas, BJ Matthews, Ritchie SA, and **LB Vosshall**. 2014. Multimodal integration of carbon dioxide and other sensory cues drives mosquito attraction to humans. Cell 156: 1060-1071 PMID: 24581501

c. McBride CS, F Baier, AB Omondi, SA Spitzer, J Lutomiah, R Sang, R Ignell, and **LB Vosshall**. 2014. Evolution of mosquito preference for humans linked to an odorant receptor. Nature 515:222-227 PMID: 25391959
d. Kistler KE, **LB Vosshall**, BJ Matthews. 2015. Genome engineering with CRISPR-Cas9 in the mosquito *Aedes aegypti*. Cell Rep 11:51-60 PMID: 25818303

Complete List of Published Work in NCBI My Bibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/leslie.vosshall.1/bibliography/47817242/public/?sort=date&direction=ascending

D. Research Support

Ongoing

HHMI Investigator Award Vosshall (PI) 07/01/08-08/31/18
Modulation of Behavior by Internal Physiological State
The goal of this study is to understand how internal physiological states alter behavior.

R01 DC014247 Vosshall (PI) 12/01/14-11/30/19
Neuropeptide Regulation of Mosquito Host-Seeking Behavior
The goal of this project is to identify neuropeptide signaling mechanisms that modulate female mosquito behavior.

2016 Advanced Proposal Vosshall (PI) 10/1/2016 - 9/30/2018
Small Molecules to Prevent Arthropod Biting Behavior
Robertson Therapeutic Development Fund
The goal of this project is to develop small molecules that inhibit biting behavior of disease-vectoring arthropods

The Quadrivium Foundation Vosshall (PI) 3/1/2017 - 2/28/2018
The Quadrivium Award for Innovative Research in Epigenetics
Epigenetic Regulation of Mosquito Behavior

Completed

R01 DC013339 Mainland (PI) 07/13/13-06/30/16
Perceptual Effects of Genetic Variation in Human Odorant Receptors
The goal of this study is to examine the relationship between variation in odorant receptor genes and human smell perception.
Role: Co-Investigator

FNIH CU08-7037 Axel (PI) 09/15/05-09/14/13
Bill and Melinda Gates Foundation Grand Challenge 8, #786
Molecular Approaches to Alter Olfactory-Driven Behaviors of Insect Disease Vectors
The goal of this project was to develop novel insect repellents that target the olfactory system of vector insects
Role: Co-Investigator

R01 DC008600 Vosshall (PI) 12/04/06-11/30/12
Molecular biology of the odorant receptors
The goal of this study was to investigate the molecular structure and function of the insect odorant receptor complex.
Role: PI

NIAID HHSN272200900039C Collins (PI) 10/01/10-09/30/12
Comparative Neurotranscriptome of *Aedes aegypti*
The goal of this project was to use RNAseq techniques with Illumina technology to decode the transcriptome of neural tissues of the yellow fever mosquito under different regimes of host-seeking behavior.
Role: Co-Investigator