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Positions

07/2012 - Present	Assistant Professor, Department of Physiology, UCSF

Education

2006	Ph.D.	Chemistry and Chemical Biology.	University of California, San Francisco
1999	B.A.	Chemistry, *magna cum laude.*	Princeton University

Training

2007–2012	Postdoctoral fellow, Rockefeller University. Advisor: Jeff Friedman, M.D. Ph.D.
2006–2007	Postdoctoral fellow, UCSF. Advisor: Kevan M. Shokat, Ph.D.
2000–2006	Graduate student, UCSF. Advisor: Kevan M. Shokat, Ph.D.

Honors and Awards

2016	Helmholtz Young Investigator in Diabetes Award
2016	Pathway Accelerator Award – American Diabetes Association
2015	NIH New Innovator Award
2014	Rita Allen Scholar Award
2014	Alfred P. Sloan Foundation Research Fellow in Neuroscience
2013	New York Stem Cell Foundation – Robertson Neuroscience Investigator Award
2013	NARSAD Young Investigator Award
2013	McKnight Technological Innovations in Neuroscience Award
2013	Klingenstein Fellowship Award in the Neurosciences
2013	Program for Breakthrough Biological Research Award - UCSF
2009	NIH Pathway to Independence Award
2007	Life Sciences Research Foundation, Postdoctoral Fellowship
2006	UCSF Krevans Distinguished Dissertation Award
2002	Grand Prize Winner, National Collegiate Inventors Competition
2001	Howard Hughes Medical Institute, Predoctoral Fellowship
2000	ARCS Foundation, Predoctoral Fellowship

Professional Activities

2009 – present	Editorial Board, *The Biochemical Journal*
2007 – 2012	Co-Founder and Scientific Advisor, *Intellikine Inc.*

Publications

From my lab at UCSF

59. Tan, C.L. and Knight, Z.A. Regulation of body temperature by the nervous system. **Neuron**, 2018 April 4.

58. Beutler, L.R and Knight, Z.A. A spotlight on appetite. **Neuron**, 2018, Feb. 21;97(4):739-741

57. Leib, D.E.*, Zimmerman, C.A.*, Poormoghaddam, A., Huey, E.L., Ahn, J.S., Lin, Y-C, Tan, C.L., Chen, Y., and Knight, Z.A. The forebrain thirst circuit drives drinking though negative reinforcement. **Neuron**, 2017, December 20;96(6):1272-1281

56. Garrison J.L. and Knight, Z.A. Linking smell to metabolism and aging. **Science**, 2017 Nov 10;358(6364):718-719. PMID: 29123049

55. Beutler, L.R.*, Chen. Y.*, Ahn J.S., Lin Y-C., Essner, R.A., and Knight, Z.A. Dynamics of gut-brain communication underlying hunger. **Neuron**, 2017 Oct 11;96(2):461-475.e5. PMID: 29024666

54. Zimmerman, C.A., Leib, D.E., and Knight, Z.A. Neural circuits underlying thirst and fluid homeostasis. **Nature Reviews Neuroscience**. 2017, Aug;18(8):459-469. PMID: 28638120.

53. Chung, S., Weber, F., Zhong, P., Tan, C.L, Nguyen, T., Beier, K.T., Hormann, N., Chang, W-C., Zhang, Z., Do, J.P., Yao, S., Krashes, M.J., Tasic, B., Cetin, A., Zeng, H., Knight, Z.A., Luo, L., Dan, Y., Identification of preoptic sleep neurons by retrograde labelling and sequencing. **Nature**. 2017. May 25;545(7655):477-481. PMID: 28514446

52. Leib, D.E., Zimmerman, C.A., and Knight, Z.A. Thirst. **Current Biology**. 2016, December 19; 26(24) R1260-R1265 PMID: 27997832

51. Tan, C.L., Cooke, E.K., Leib, D.E., Lin, Y-C., Daly, G.E., Zimmerman, C.A., and Knight, Z.A. Warm-sensitive neurons that control body temperature. **Cell**. 2016, September 22; 167(1):47-59 PMID: 27616062 PMCID: PMC5062957

50. Chen, Y., Lin, Y-C., Zimmerman, C.A., Essner, R.A., and Knight, Z.A. Hunger neurons drive feeding through a sustained, positive reinforcement signal. **eLife**. 2016, August 24;5. pii: e18640. doi: 10.7554/eLife.18640. PMID: 27554486 PMCID: PMC5016090

49. Leib, D.E., and Knight, Z.A. Rapid sensing of dietary amino acid deficiency does not require GCN2. **Cell Reports**. 2016, August 23; 16(8): 2051-2. PMID: 27558825

48. Zimmerman, C.A., Lin, Y.C., Leib, D.E., Guo, L., Daly, G., Chen, Y, and Knight, Z.A., Thirst neurons anticipate the homeostatic consequences of eating and drinking. **Nature**, 2016, August 3; 3;537(7622): 680-684 PMID: 27487211

47. Chen, Y. and Knight, Z.A., Making sense of the sensory regulation of hunger neurons. **Bioessays**, 2016, April 4;38(4):316-24; PMID: 26898524

46. Leib, D.E., and Knight, Z.A. Reexamination of dietary amino acid sensing reveals a GCN2-independent mechanism. **Cell Reports**. 2015 November 10; 13(6):1081-9; PMID: 26526991

45. Chen, Y., Lin, Y.C., Kuo, T.W. and Knight, Z.A., Sensory detection of food rapidly modulates arcuate feeding circuits. **Cell**, 2015. February 26; 160(5):829-41. PMID: 25703096 PMCID: PMC4373539

Earlier work

44. Knight, Z.A.*****, Schmidt, S.*, Birsoy, K., Tan, K., Friedman, J.M., A critical role for mTORC1 in erythropoiesis and anemia, **eLife**. 2014 Sep 8;3:e01913. PMID: 25201874 PMCID: PMC4179304

43. Tan, K., Knight, Z.A., and Friedman J.M. Ablation of AgRP neurons impairs adaptation to scheduled feeding, **Molecular Metabolism**, 2014 Jul 10;3(7):694-704. PMID: 25352998 PMCID: PMC4209355

42. Ekstrand, M.I.*, Nectow, A.R.*, Knight, Z.A., Latcha, K.N., Pomeranz, L.E., and Friedman, J.M., Molecular profiling of neurons based on connectivity. **Cell**, 2014 May 22;157(5):1230-42

41. Knight, Z.A., Tan, K., Birsoy, K., Schmidt, S., Garrison, J.L., Wysocki, R.W., Emiliano, A., Ekstrand, M.I., and Friedman, J.M., Molecular profiling of activated neurons by phosphorylated ribosome capture, **Cell**. 2012, November 21; 151(5): 1126-37. PMID: 23178128

40. Knight, Z.A., For a PDK1 inhibitor, the substrate matters, **Biochemical Journal**. 2011, January 15; 433(2):1-2.

39. Knight, Z.A., Hannan, K.S., Greenberg, M., and Friedman, J.M., Hyperleptinemia is required for the development of leptin resistance, **PLoS One**. 2010, June; 5(6):1-8.

38. Knight, Z.A. Small molecule inhibitors of the PI3-kinase family, **Phosphoinositide 3-kinase in Health and Disease: Current Topics in Microbiology and Immunology.** 2010, May 7; 346:

37. Williams, O., Houseman, B.T., Kunkel, E.J., Aizenstein, B., Hoffman, R., Knight, Z.A., and Shokat K.M., Discovery of dual inhibitors of the immune cell PI3-Ks p110delta and p110gamma inhibitors: a prototype for new anti-inflammatory drugs, **Chemistry & Biology**. 2010, February 26; 17(2):123-134.

36. Knight, Z.A., Lin, H., Shokat, K.M., Targeting the cancer kinome through polypharmacology, **Nature Reviews Cancer.** 2010, February; 10(2):130-137.

35. Niedermeier, M., Hennessy, B.T., Knight, Z.A., Henneberg, M., Hu, J., Kurtova, A.V., Wierda, W.G., Keating, M.J., Shokat, K..M., and Burger, J.A. Isoform-selective phosphoinositide 3'-kinase inhibitors inhibit CXCR4 signaling and overcome stromal cell-mediated drug resistance in chronic lymphocytic leukemia: a novel therapeutic approach, **Blood.** 2009, May 28; 113(22):5549-57.

34. Fan, Q.W., Cheng, C., Knight, Z.A., Haas-Kogan, D., Stokoe, D., James, C.D., McCormick, F., Shokat, K.M., and Weiss, W.A. EGFR signals to mTOR through PKC and independently of Akt in glioma, **Science Signaling**. 2009, January 27; 2(55):1-9.

33. Feldman, M.E., Apsel, B.A., Uotila, A., Loewith, R., Knight, Z.A., Ruggero D., Shokat, K.M., Active site inhibitors of mTOR target rapamycin-resistant outputs of mTORC1 and mTORC2, **PLoS Biology.** 2009, February; 7(2):e38.

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26. Zunder, E.R., Knight, Z.A., Houseman, B.T., Apsel, B., and Shokat, K.M., Discovery of drug-resistant and drug-sensitizing mutations in the oncogenic PI3K isoform p110alpha, **Cancer Cell**. 2008, August 12; 14(2):180-192.

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21. Chen, J.S., Zhou, L.J., Entin-Meer, M., Yang. X., Donker, M., Knight, Z.A., Weiss, W., Shokat, K.M., Haas-Kogan, D., and Stokoe, D. Characterization of structurally distinct, isoform-selective phosphoinositide 3'-kinase inhibitors in combination with radiation in the treatment of glioblastoma, **Molecular Cancer Therapeutics.** 2008, April; 7(4):841-850.

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19. Balla, A., Kim, Y.J., Varnai, P., Szentpetery, Z., Knight, Z.A., Shokat, K.M., and Balla, T. Maintenance of hormone sensitive phosphoinositide pools in the plasma membrane requires phosphatidylinositol 4-kinase III alpha, **Molecular Biology of the Cell**. 2008 February; 19(2):711-721.

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17. Knight, Z.A., Garrison, J.L., Chan, K., King, D.S., Shokat, K.M. A remodelled protease that cleaves phosphotyrosine substrates, **Journal of the American Chemical Society**. 2007, September 6; 129(38):11672-11673.

16. Fan, Q-W., Cheng, C.K., Nicolaides, T.P., Hackett, C.S., Knight, Z.A., Shokat, K.M., and Weiss, W.A. A dual phosphoinositide-3-kinasealpha/mTOR inhibitor cooperates with blockade of epidermal growth factor receptor in PTEN-mutant glioma, **Cancer Research**. 2007, September 1; 67(17):7960-7965.

15. Hung, C-H., Thomas, L., Ruby, C.E., Atkins, K.M., Morris, N.P., Knight, Z.A., Scholz, I. Barklis, E., Weinberg, A.D., Shokat, K.M., and Thomas, G. HIV-1 Nef assembles a Src family kinase—ZAP-70/Syk—PI3K cascade to downregulate cell surface MHC-I, **Cell Host & Microbe**. 2007, April 19; 1:121-133.

14. Knight, Z.A. and Shokat, K.M. Chemical genetics: Where genetics and pharmacology meet, **Cell**. 2007, February 9; 128(3):425-430.

13. Knight, Z.A. and Shokat, K.M. Chemically targeting the PI3-kinase family, **Biochemical Society Transactions.** 2007, April; 35(2):245-249.

12. Toth, B., Balla, A., Hui, M., Knight, Z.A., Shokat, K.M., and Balla, T. Phosphatidylinositol 4-kinase IIIbeta regulates the transport of ceramide between the endoplasmic reticulum and Golgi, **Journal of Biological Chemistry**. 2006, November 24; 281(47):36369-36377.

11. Van Keymeulen, A., Wong, K., Knight, Z.A., Govaerts, C., Hahn, K.M., Shokat, K.M. and Bourne, H.R. To stabilize neutrophil polarity, PIP3 and Cdc42 augment RhoA activity at the back as well as signals at the front, **Journal of Cell Biology**. 2006, July 31; 174(3):437-445.

10. Knight, Z.A., Gonzalez-Perez, B., Feldman, M.E., Zunder, E.R., Goldenberg, D.D., Williams, O., Stokoe, D., Balla, A., Toth, B., Balla, T., Loewith, R., Weiss W.A., Williams, R.L. and Shokat, K.M. A pharmacological map of the PI3-K family defines a role for p110alpha in insulin signaling, **Cell**. 2006, May 19; 125(4):733-747.

9. Fan, Q.W., Knight, Z.A., Goldenberg, D.A., Yu, W., Mostov, KE., Stokoe, D., Weiss, W.A. and Shokat, K.M. A dual PI3-kinase/mTOR inhibitor reveals emergent efficacy in glioma, **Cancer Cell**. 2006, May; 9(5):341-349.

8. Sturgeon C.M., Knight, Z.A., Shokat, K.M. and Roberge, M. Effect of combined DNA repair inhibition and G2 checkpoint inhibition on cell cycle progression after DNA damage, **Molecular Cancer Therapeutics**. 2006, April; 5(4):885-892

7. Knight, Z.A. and Shokat K.M. Knock-outs and inhibitors: one in the same?, **Blood**, 2006, January 15; 107(2):420-421.

6. Knight, Z.A. and Shokat K.M. Features of selective kinase inhibitors, **Chemistry and Biology**. 2005, June; 12:621-637.

5. Alaimo, P.J.*, Knight Z.A*. and Shokat K.M. Targeting the gatekeeper residue in phosphoinositide 3-kinases, **Bioorganic and Medicinal Chemistry**. 2005, April 15; 13(8):2825-2836. * equal contributions

4. Knight, Z.A., Chang, G.C., Alaimo, P.J., Kenski, D.M., Ho, C.B., Abraham, R.T. and Shokat, K.M. Isoform-specific phosphoinositide 3-kinase inhibitors from an arylmorpholine scaffold, **Bioorganic and Medicinal Chemistry**. 2004, August 15; 12(17):4749-4759.

3. Knight, Z.A., Schilling, B., Row, R.H., Gibson, B.W., Kenski, D.M. and Shokat, K.M. Phosphospecific proteolysis for mapping sites of protein phosphorylation, **Nature Biotechnology**. 2003, September; 21(9):1047-1054.

2. Tzfati, Y., Knight, Z.A., Roy, J. and Blackburn, E.H. A novel pseudoknot element is essential for the action of a yeast telomerase, **Genes and Development**. 2003, July 15; 17(14):1779-1788.

1. Knight, Z.A. Another possible mechanism of resistance to STI571. **Blood**. 2000, Dec 1; 96(12):4003-4005.

Patents

Friedman, J.M., Knight, Z.A., Birsoy, K., Tan, K. Methods and compositions for activity dependent transcriptome profiling. US 14/399,057. November 5, 2014.

Knight, Z.A., Apsel, B.A., Shokat, K.M. Substituted pyrazolo-3,4-pyrimidines as kinase antagonists. US 7,585,868. September 8, 2009.

Knight, Z.A., Apsel, B.A., Shokat, K.M. Substituted pyrazolo[3,2-d]pyrimidines as anti-cancer agents. US 8,642,604. July 24, 2009.

Research Narrative

My laboratory studies the neurobiology of homeostasis, including especially the mechanisms that control hunger, thirst, and body temperature. Our goal is to elucidate the structure and dynamics of the underlying neural circuits, so that we can begin to understand how these circuits sense the physical needs of the body, translate those needs into motivated behaviors, and further become dysregulated in conditions such as obesity. This research program builds on my work as a postdoctoral fellow, where I developed new technologies that enable the use of RNA sequencing to molecularly profile neurons that have specific activity patterns (Knight, Z.A., et al, *Cell*, 2012) or connectivity (Ekstrand, M.I., et al., *Cell*, 2014). My lab has used these tools to discover new populations of neurons in the mouse brain that control homeostatic behaviors, and we are currently studying these cells and their associated circuits using a variety of genetic, optical and physiologic approaches. In 2015, my lab reported the in vivo dynamics of the key neurons in the mouse brain that control hunger and the unexpected discovery that these neurons are rapidly regulated by the sensory detection of food (Chen, Y., et al., *Cell*, 2015). We later showed that these cells regulate feeding through an unusual "sustained hunger signal" (Chen. Y.,et al, *eLife*, 2016) and further that they receive rapid signals from the gut during feeding that relay the calorie content of food (Beutler, L.B., et al., *Neuron*, 2017). In 2016, we reported the in vivo dynamics of key neurons that control thirst, and the surprising discovery that these cells are rapidly regulated by signals from the oral cavity during eating and drinking (Zimmerman, C.A. et al., *Nature*, 2016). We subsequently identified the neurons downstream of these cells, and showed that thirst circuit as a whole drives drinking via the common mechanism of negative reinforcement (Leib. D.E., et al, *Neuron*, 2017). In 2016 we described identification of the elusive warm-sensitive neurons of the preoptic hypothalamus, which are thought to be the key neurons in the brain that control body temperature (Tan, C.L. et al., *Cell*, 2016). An ongoing interest of the lab is to understand how these and other homeostatic circuits integrate sensory information from the outside world with internal signals arising from the body in order to generate and shape goal-directed behaviors such as feeding and drinking.