GU4088: Seminar in Neurobiochemistry and Neurological Diseases

Fall 2023

Time: Tuesday 4:10 – 6:00

Location: 800 Fairchild

Instructor: Jian Yang email: jy160@columbia.edu

Course description:

Students will read and discuss classical as well as contemporary research papers on the molecular and cellular mechanisms of membrane excitability, synaptic transmission and sensory transduction, and the pathogenic mechanisms and therapeutics of certain neurological diseases related to these processes. Focus will be on intellectual creativity, conceptual breakthroughs, and technical advances. A key goal of the course is to help students become a critical reader and thinker.

Graduate students in all disciplines are welcome. Advanced undergraduate students can enroll with instructor's permission.

For PhD students in the Biological Sciences Program, this is a tier 3 course.

Prerequisites:

One year of introductory biology and UN3004/GU4004 "Cellular and Molecular Neurobiology" (or equivalent).

Course schedule:

* Marks supplemental readings that provide more background/context on the relevant topics. They are not required and will not be discussed in detail in class but may help you better understand and get more out of the selected papers.

Sept. 5. Session 1. Introduction[1]

Altimus, C.M. et al. The Next 50 Years of Neuroscience. *Journal of Neuroscience* **40**, 101-106 (2020).

Sept. 12. Session 2. Biochemistry and structural basis of K+ channel ion selectivity[2,3]

Doyle, D.A. et al. The structure of the potassium channel: Molecular basis of K+ conduction and selectivity. *Science* **280**, 69-77 (1998).

Zhou, Y.F., Morais-Cabral, J.H., Kaufman, A. & MacKinnon, R. Chemistry of ion coordination and hydration revealed by a K+ channel-Fab complex at 2.0 angstrom resolution. *Nature* **414**, 43-48 (2001).

Sept. 19. Session 3. Molecular mechanisms of olfaction[4-6]

Buck, L. & Axel, R. A Novel Multigene Family May Encode Odorant Receptors - a Molecular-Basis for Odor Recognition. *Cell* **65**, 175-187 (1991).

Zhao, H.Q. et al. Functional expression of a mammalian odorant receptor. *Science* **279**, 237-242 (1998).

Mombaerts, P. et al. Visualizing an olfactory sensory map. *Cell* **87**, 675-686 (1996).

Sept. 26. Session 4. Receptors and coding logic for taste[7-10]

Zhao, G.Q. et al. The receptors for mammalian sweet and umami taste. *Cell* **115**, 255-266 (2003).

Zhang, Y.F. et al. Coding of sweet, bitter, and umami tastes: Different receptor cells sharing similar signaling pathways. *Cell* **112**, 293-301 (2003).

Mueller, K.L. et al. The receptors and coding logic for bitter taste. *Nature* **434**, 225-229 (2005).

Huang, A.L. et al. The cells and logic for mammalian sour taste detection. *Nature* **442**, 934-938 (2006).

Oct. 3. Session 5. The discovery of SNARES[11-14]

Sollner, T. et al. Snap Receptors Implicated in Vesicle Targeting and Fusion. *Nature* **362**, 318-324 (1993).

Sollner, T., Bennett, M.K., Whiteheart, S.W., Scheller, R.H. & Rothman, J.E. A Protein Assembly-Disassembly Pathway in-Vitro That May Correspond to Sequential Steps of Synaptic Vesicle Docking, Activation, and Fusion. *Cell* **75**, 409-418 (1993).

Debello, W.M. et al. Snap-Mediated Protein-Protein Interactions Essential for Neurotransmitter Release. *Nature* **373**, 626-630 (1995).

*Hussain, S. & Davanger, S. The Discovery of the Soluble N-Ethylmaleimide-Sensitive Factor Attachment Protein Receptor Complex and the Molecular Regulation of Synaptic Vesicle Transmitter Release: The 2010 Kavli Prize in Neuroscience. *Neuroscience* **190**, 12-20 (2011).

Oct. 10. Session 6. Silent synapses and their roles in addiction[15-18]

Liao, D.Z., Hessler, N.A. & Malinow, R. Activation of Postsynaptically Silent Synapses during Pairing-Induced Ltp in Ca1 Region of Hippocampal Slice. *Nature* **375**, 400-404 (1995).

Isaac, J.T.R., Nicoll, R.A. & Malenka, R.C. Evidence for Silent Synapses - Implications for the Expression of Ltp. *Neuron* **15**, 427-434 (1995).

Wang, Y.Q. et al. AMPA and NMDA Receptor Trafficking at Cocaine-Generated Synapses. *Journal of Neuroscience* **41**, 1996-2011 (2021).

*Vincent-Lamarre, P., Lynn, M. & Beique, J.C. The Eloquent Silent Synapse. *Trends in Neurosciences* **41**, 557-559 (2018).

Oct. 17. No class (International ion channel conference)

Oct. 24. Session 7. Proteostatic regulation[19-22]

Kang, H. & Schuman, E.M. A requirement for local protein synthesis in neurotrophin-induced hippocampal synaptic plasticity. *Science* **273**, 1402-6 (1996).

Hafner, A.S., Donlin-Asp, P.G., Leitch, B., Herzog, E. & Schuman, E.M. Local protein synthesis is a ubiquitous feature of neuronal pre- and postsynaptic compartments. *Science* **364**, 650-+ (2019).

Donlin-Asp, P.G., Polisseni, C., Klimek, R., Heckel, A. & Schuman, E.M. Differential regulation of local mRNA dynamics and translation following long-term potentiation and depression. *Proceedings of the National Academy of Sciences of the United States of America* **118**(2021).

*Giandomenico, S.L., Alvarez-Castelao, B. & Schuman, E.M. Proteostatic regulation in neuronal compartments. *Trends Neurosci* **45**, 41-52 (2022).

Oct. 31. Session 8. Development of optogenetics[23-26]

Nagel, G. et al. Channelrhodopsin-2, a directly light-gated cation-selective membrane channel. *Proceedings of the National Academy of Sciences of the United States of America* **100**, 13940-13945 (2003).

Boyden, E.S., Zhang, F., Bamberg, E., Nagel, G. & Deisseroth, K. Millisecond-timescale, genetically targeted optical control of neural activity. *Nature Neuroscience* **8**, 1263-1268 (2005).

Zhang, F. et al. Multimodal fast optical interrogation of neural circuitry. *Nature* **446**, 633-U4 (2007).

*Fischer, A.A.M., Kramer, M.M., Radziwill, G. & Weber, W. Shedding light on current trends in molecular optogenetics. *Current Opinion in Chemical Biology* **70**(2022).

Nov. 7. No class (election day)

Nov. 14. Session 9. Application of optogenetics in neurological diseases[27-29]

Tonnesen, J., Sorensen, A.T., Deisseroth, K., Lundberg, C. & Kokaia, M. Optogenetic control of epileptiform activity. *Proc Natl Acad Sci U S A* **106**, 12162-7 (2009).

Lin, D. et al. Functional identification of an aggression locus in the mouse hypothalamus. *Nature* **470**, 221-6 (2011).

Chaudhury, D. et al. Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. *Nature* **493**, 532-6 (2013).

Nov. 21. Session 10. Microglia in health and disease[30-33]

Davalos, D. et al. ATP mediates rapid microglial response to local brain injury in vivo. *Nat Neurosci* **8**, 752-8 (2005).

Parkhurst, C.N. et al. Microglia Promote Learning-Dependent Synapse Formation through Brain-Derived Neurotrophic Factor. *Cell* **155**, 1596-1609 (2013).

Hong, S. et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science* **352**, 712-716 (2016).

*Sierra, A., Paolicelli, R.C. & Kettenmann, H. Cien Anos de Microglia: Milestones in a Century of Microglial Research. *Trends Neurosci* **42**, 778-792 (2019).

Nov. 28. Session 11. Magnetic protein biocompass and magnetogenetics[34-39]

Qin, S. et al. A magnetic protein biocompass. *Nat Mater* **15**, 217-26 (2016).

Long, X., Ye, J., Zhao, D. & Zhang, S.J. Magnetogenetics: remote non-invasive magnetic activation of neuronal activity with a magnetoreceptor. *Sci Bull (Beijing)* **60**, 2107-2119 (2015).

Pang, K.L. et al. MagR Alone Is Insufficient to Confer Cellular Calcium Responses to Magnetic Stimulation. *Frontiers in Neural Circuits* **11**(2017).

*Meister, M. Physical limits to magnetogenetics. *Elife* **5**(2016).

*Nimpf, S. & Keays, D.A. Myths in magnetosensation. *Iscience* **25**(2022).

*Xie, C. Searching for unity in diversity of animal magnetoreception: From biology to quantum mechanics and back. *Innovation* **3**(2022).

Dec. 5. Session 12. Magnetoreception [38-42] (This session is one and half hours)

Gegear, R.J., Casselman, A., Waddell, S. & Reppert, S.M. Cryptochrome mediates light-dependent magnetosensitivity in Drosophila. *Nature* **454**, 1014-8 (2008).

Gegear, R.J., Foley, L.E., Casselman, A. & Reppert, S.M. Animal cryptochromes mediate magnetoreception by an unconventional photochemical mechanism. *Nature* **463**, 804-7 (2010).

Foley, L.E., Gegear, R.J. & Reppert, S.M. Human cryptochrome exhibits light-dependent magnetosensitivity. *Nat Commun* **2**, 356 (2011).

Hochstoeger, T. et al. The biophysical, molecular, and anatomical landscape of pigeon CRY4: A candidate light-based quantal magnetosensor. *Science Advances* **6**(2020).

Xu, J. et al. Magnetic sensitivity of cryptochrome 4 from a migratory songbird. *Nature* **594**, 535-540 (2021).

*Nimpf, S. & Keays, D.A. Myths in magnetosensation. *Iscience* **25**(2022).

*Xie, C. Searching for unity in diversity of animal magnetoreception: From biology to quantum mechanics and back. *Innovation* **3**(2022).

Class format:

In each session, a designated student will give a 45-minute presentation on the assigned papers, discussing background, major findings, conclusions, and unresolved issues. This is followed by an in-depth discussion involving the whole class. Depending on enrollment, each student will give one or two presentations.

Weekly homework:

Read the assigned papers in advance. Write 10 questions and answers on the papers. Submit the Q&As to me (jy160@columbia.edu) by email no later than midnight of Monday.

Final exam:

Write a research proposal on the “Molecular and Cellular Mechanisms of Itch”. The focus should be on peripheral components and processes – genes, receptors, channels, markers, cells, transduction, coding, etc. Do not propose projects on detection and processing in the brain. The proposal must be completed independently by yourself but you are allowed to read and synthesize any materials that you deem relevant and appropriate.

Requirements for the proposal: total 5 pages (references not included), single space, 12 size font, 1 inch margin. A maximum of 4 figures/graphs are allowed.

Only two sections are required: **introduction** and **experimental design**. The latter section should constitute >70% of the proposal; this is the meat of your proposal. Clearly describe your hypothesis, rationale, specific step-by-step experimental design, potential outcomes and interpretations, and alternative approaches (e.g., if this does not work, I'll try that). No need to describe any methods in detail - I assume you know the methods and have the necessary equipment. What I am looking for is creativity, novelty, logic, depth and width of your knowledge (or reading) and thinking, feasibility, and practicality.

Grading:

The weekly homework, the final exam and class participation (your presentation and participation) count 30%, 35% and 35%, respectively, toward the final grade.

1. Altimus, C.M. et al. The Next 50 Years of Neuroscience. *Journal of Neuroscience* **40**, 101-106 (2020).
2. Doyle, D.A. et al. The structure of the potassium channel: Molecular basis of K+ conduction and selectivity. *Science* **280**, 69-77 (1998).
3. Zhou, Y.F., Morais-Cabral, J.H., Kaufman, A. & MacKinnon, R. Chemistry of ion coordination and hydration revealed by a K+ channel-Fab complex at 2.0 angstrom resolution. *Nature* **414**, 43-48 (2001).
4. Buck, L. & Axel, R. A Novel Multigene Family May Encode Odorant Receptors - a Molecular-Basis for Odor Recognition. *Cell* **65**, 175-187 (1991).
5. Zhao, H.Q. et al. Functional expression of a mammalian odorant receptor. *Science* **279**, 237-242 (1998).
6. Mombaerts, P. et al. Visualizing an olfactory sensory map. *Cell* **87**, 675-686 (1996).
7. Zhao, G.Q. et al. The receptors for mammalian sweet and umami taste. *Cell* **115**, 255-266 (2003).
8. Zhang, Y.F. et al. Coding of sweet, bitter, and umami tastes: Different receptor cells sharing similar signaling pathways. *Cell* **112**, 293-301 (2003).
9. Mueller, K.L. et al. The receptors and coding logic for bitter taste. *Nature* **434**, 225-229 (2005).

10. Huang, A.L. et al. The cells and logic for mammalian sour taste detection. *Nature* **442**, 934-938 (2006).
11. Sollner, T., Bennett, M.K., Whiteheart, S.W., Scheller, R.H. & Rothman, J.E. A Protein Assembly-Disassembly Pathway in-Vitro That May Correspond to Sequential Steps of Synaptic Vesicle Docking, Activation, and Fusion. *Cell* **75**, 409-418 (1993).
12. Sollner, T. et al. Snap Receptors Implicated in Vesicle Targeting and Fusion. *Nature* **362**, 318-324 (1993).
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14. Hussain, S. & Davanger, S. The Discovery of the Soluble N-Ethylmaleimide-Sensitive Factor Attachment Protein Receptor Complex and the Molecular Regulation of Synaptic Vesicle Transmitter Release: The 2010 Kavli Prize in Neuroscience. *Neuroscience* **190**, 12-20 (2011).
15. Liao, D.Z., Hessler, N.A. & Malinow, R. Activation of Postsynaptically Silent Synapses during Pairing-Induced Ltp in Ca1 Region of Hippocampal Slice. *Nature* **375**, 400-404 (1995).
16. Isaac, J.T.R., Nicoll, R.A. & Malenka, R.C. Evidence for Silent Synapses - Implications for the Expression of Ltp. *Neuron* **15**, 427-434 (1995).
17. Wang, Y.Q. et al. AMPA and NMDA Receptor Trafficking at Cocaine-Generated Synapses. *Journal of Neuroscience* **41**, 1996-2011 (2021).
18. Vincent-Lamarre, P., Lynn, M. & Beique, J.C. The Eloquent Silent Synapse. *Trends in Neurosciences* **41**, 557-559 (2018).
19. Kang, H. & Schuman, E.M. A requirement for local protein synthesis in neurotrophin-induced hippocampal synaptic plasticity. *Science* **273**, 1402-6 (1996).
20. Hafner, A.S., Donlin-Asp, P.G., Leitch, B., Herzog, E. & Schuman, E.M. Local protein synthesis is a ubiquitous feature of neuronal pre- and postsynaptic compartments. *Science* **364**, 650-+ (2019).
21. Donlin-Asp, P.G., Polisseni, C., Klimek, R., Heckel, A. & Schuman, E.M. Differential regulation of local mRNA dynamics and translation following long-term potentiation and depression. *Proceedings of the National Academy of Sciences of the United States of America* **118**(2021).
22. Giandomenico, S.L., Alvarez-Castelao, B. & Schuman, E.M. Proteostatic regulation in neuronal compartments. *Trends Neurosci* **45**, 41-52 (2022).
23. Nagel, G. et al. Channelrhodopsin-2, a directly light-gated cation-selective membrane channel. *Proceedings of the National Academy of Sciences of the United States of America* **100**, 13940-13945 (2003).
24. Boyden, E.S., Zhang, F., Bamberg, E., Nagel, G. & Deisseroth, K. Millisecond-timescale, genetically targeted optical control of neural activity. *Nature Neuroscience* **8**, 1263-1268 (2005).
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26. Fischer, A.A.M., Kramer, M.M., Radziwill, G. & Weber, W. Shedding light on current trends in molecular optogenetics. *Current Opinion in Chemical Biology* **70**(2022).
27. Tonnesen, J., Sorensen, A.T., Deisseroth, K., Lundberg, C. & Kokaia, M. Optogenetic control of epileptiform activity. *Proc Natl Acad Sci U S A* **106**, 12162-7 (2009).
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32. Hong, S. et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science* **352**, 712-716 (2016).
33. Sierra, A., Paolicelli, R.C. & Kettenmann, H. Cien Anos de Microglia: Milestones in a Century of Microglial Research. *Trends Neurosci* **42**, 778-792 (2019).
34. Qin, S. et al. A magnetic protein biocompass. *Nat Mater* **15**, 217-26 (2016).
35. Long, X., Ye, J., Zhao, D. & Zhang, S.J. Magnetogenetics: remote non-invasive magnetic activation of neuronal activity with a magnetoreceptor. *Sci Bull (Beijing)* **60**, 2107-2119 (2015).
36. Pang, K.L. et al. MagR Alone Is Insufficient to Confer Cellular Calcium Responses to Magnetic Stimulation. *Frontiers in Neural Circuits* **11**(2017).
37. Meister, M. Physical limits to magnetogenetics. *Elife* **5**(2016).
38. Nimpf, S. & Keays, D.A. Myths in magnetosensation. *Iscience* **25**(2022).
39. Xie, C. Searching for unity in diversity of animal magnetoreception: From biology to quantum mechanics and back. *Innovation* **3**(2022).
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42. Foley, L.E., Gegear, R.J. & Reppert, S.M. Human cryptochrome exhibits light-dependent magnetosensitivity. *Nat Commun* **2**, 356 (2011).
43. Hochstoeger, T. et al. The biophysical, molecular, and anatomical landscape of pigeon CRY4: A candidate light-based quantal magnetosensor. *Science Advances* **6**(2020).
44. Xu, J. et al. Magnetic sensitivity of cryptochrome 4 from a migratory songbird. *Nature* **594**, 535-540 (2021).