BIPN194 Advanced Topics in Modern Biology: Synapse and Autism

Class meeting time and location: Fridays 3:00pm-4:30pm, YORK 3010

Professor Yishi Jin
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[please include BIPN194 in subject line of any emails concerning the class]

Office Hours: Mon 9-10:30 AM at 2418 Bonner Hall, and by appointment.

Outline of the course:

April 3: Introduction lecture on synapses, class organization and assignment of discussion groups.

April 10: presynaptic terminal/group I

April 17: postsynaptic terminal/group 2

April 24: synaptic adhesion/group 3

May 1: autism genetics/group 4

May 8: Shank in autism/group 5

May 15 Cntnap2 in autism/group 6

May 22: Neuroligin in autism/group 7

May 29: Fragile X in autism/group 8

June 5: Novel animal models/group 9

Prerequisites: *This course will assume upper division knowledge of genetics, cell biology, molecular biology and neurobiology.* BICD100 (genetics), BICD (Cell Biology), BIPN 100 (Mammalian Physiology), and BIPN144 (neural development) or BIPN142 (cellular neuroscience) are strongly recommended.

Course Description

Synapses are where the actions in the nervous system take place! Many neurological diseases are associated with synapse dysfunction. Recent genetic studies of Autism or Autism spectral disorders (ASD) have implicated many mutations affecting genes that function in synapses. The goals of the course are to provide basic knowledge on how synapses are formed and regulated, and to discuss cutting-edge research on understanding the causative associations of genes in Autism. Specifically, we will first focus on the key studies that reveal the tripartite components of the synapse. We will

then discuss representative research on understanding autism-associated genetic mutations on synapses and behaviors using animal models.

With the exception of the first introductory lecture, the meetings in this course will be student-led discussions of primary research literature. The course is highly interactive, and everyone must speak and give feedback to each other!

Evaluation. There is NO final exam. Your grade will be based on four equal components:
(1) Your performance in your group's presentation of the paper.
(2) Your attendance and audible participation in discussions.
(3) Your summaries of the papers when you are not presenting. These are due in class at the beginning of the meeting. Late hand-in will not be accepted.
(4) Your final report (2 pages) on class readings.

Reading
All reading materials are research papers and scholarly reviews, which are freely available online. We will go over how to find the papers via Pubmed or Google Scholar (scholar.google.com) in the first meeting. In some cases you will need to use a UCSD IP address to access the file. PDFs are convenient ways to read the papers; hard copies will not be provided. For your presentations of figures, the html files may be more useful.

There is no textbook for this course. Use your textbooks from other classes (such as BISP140/142) for background information. Scholar review articles are provided to help understanding the background of the research.

Expect to spend at least 4 hours a week on the reading, more if you are presenting a paper.

Group presentations
PRESENTERS:
Each of you is a member of a group that will make a 45-minute presentation on one of the assigned research papers. This includes approximately 35 minutes for the presentation and 10 minutes for questions and discussion. Each member of the group should be prepared to answer questions or engage in discussion of their portion of the presentation.

NONPRESENTERS:
You are expected to read EVERY paper before coming to class and to be prepared to discuss it. At the beginning of the class you will turn in a summary of the paper (one-page single-space). During the presentation and discussion you are expected to participate actively. After each presentation (except your own), you will write a short evaluation of the presentation and discussion.

PRESENTATION FORMAT
Each member of a group should prepare between 2-5 powerpoint slides; handouts and chalkboard drawings are also helpful to facilitate long-term memory. The entire

presentation (made as powerpoint or keynote or other format) should be on one computer. Presenting group should arrive 10 minutes early to set up.

PRESENTATION CONTENT

1. *Background/Introduction*: What is the *biological problem*? What are the authors attempting to show? How does this work fit into the overall field? What tools are going to be used to approach the problem?
2. *Results /data*: recommend that each group member present one or two Figures/tables each. For each Figure or experiment, address (a) what is being shown, and (b) why was this experiment done, in the context of the paper. Discuss reservations or questions you have about the data. It is required that you read all the data, including those in "supplemental information", which is often in a separate file from the pdf of the article.
3. *Conclusions:* What are the conclusions? What is the model? What are the 'next steps' or remaining questions?

GROUP MEETINGS PRIOR TO PRESENTATION

It is essential that all members of the group meet prior to the presentation. I suggest group members exchange phone numbers and e-mail addresses and arrange to meet at least twice. The papers are complicated, and the level of background within the class varies. By working as a team you can give an effective presentation. I will meet with the entire group to discuss questions and presentation.

SUMMARY/EVALUATIONS OF PAPERS

At the beginning of class, the non-presenters will turn in a summary of the paper to be discussed. This should be both a brief *summary* of the paper and also an *evaluation* of how well the authors support their claims. (There is no need for statements about how hard or confusing the papers are.) Although the summary must be your own work you can discuss the papers among yourselves.

These summaries should be typed, between half to 1 page, single line spacing.
I DO NOT accept emailed summaries.

PEER EVALUATIONS

After each presentation, non-presenters will fill out a short evaluation of the presentation. Did the presentation and discussion clarify the work? Were your questions answered? Do you have suggestions for improving the quality of the presentations? This is a very important factor in your course participation.

ATTENDANCE

You are expected to attend ALL class meetings. Acceptable excuses for missing a class are: documented medical emergency and family emergency; university sponsored events.
Vacation, missing the bus, oversleeping, or deadlines or demands from other courses/exams are not acceptable excuses for missing this class.

READING LIST (download pdf from PubMed: http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=search&db=pubmed)

General information for entire course

The genetics of **autistic** disorders and its clinical relevance: a **review** of the literature. **Freitag CM**. Mol Psychiatry. 2007 Jan;12(1):2-22. Epub 2006 Oct 10. **Review**.

The neurobiology of **autism**. Pardo CA, Eberhart CG. Brain Pathol. 2007 Oct;17(4):434-47. Review.

The autism sequencing consortium: large-scale, high-throughput sequencing in autism spectrum disorders. **Buxbaum** JD, Daly MJ, Devlin B, Lehner T, Roeder K, State MW; Autism Sequencing Consortium. Neuron. 2012 Dec 20;76(6):1052-6.

Progress toward treatments for synaptic defects in autism. **Delorme R**, **Ey E**, **Toro R**, Leboyer M, Gillberg C, Bourgeron T. Nat Med. 2013 Jun;19(6):685-94.

Discussion papers:

April 10: presynaptic terminal/group I

Background reading:

Ultrastructural organization of presynaptic terminals. **Siksou** L, **Triller A**, Marty S. Curr Opin Neurobiol. 2011 Apr;21(2):261-8.

A molecular machine for neurotransmitter **release**: **synaptotagmin** and beyond. Südhof TC. Nat Med. 2013 Oct;19(10):1227-31.

Discussion paper:

Synaptotagmin I: a major Ca2+ sensor for transmitter **release** at a central synapse.

Geppert M, Goda Y, Hammer RE, Li C, Rosahl TW, Stevens CF, Südhof TC. Cell. 1994 Nov 18;79(4):717-27.

April 17: postsynaptic terminal/group 2

Background reading:

The **Shank** family of scaffold proteins. Sheng M, Kim E. J Cell Sci. 2000 Jun;113 (Pt 11):1851-6.

Discussion paper:

A preformed complex of postsynaptic proteins is involved in excitatory **synapse development**.

Gerrow K, Romorini S, Nabi SM, Colicos MA, Sala C, El-Husseini A. Neuron. 2006 Feb 16;49(4):547-62.

April 24: synaptic adhesion/group 3

Background reading:

Neuroligins and neurexins link synaptic function to cognitive disease. Südhof TC. Nature. 2008 Oct 16;455(7215):903-11.

Discussion paper:

Neurexin mediates the assembly of presynaptic terminals. Dean C, Scholl FG, Choih J, DeMaria S, Berger J, Isacoff E, **Scheiffele** P. Nat Neurosci. 2003 Jul;6(7):708-16.

May 1: autism genetics/group 4

Background reading:

The autism sequencing consortium: large-scale, high-throughput sequencing in autism spectrum disorders. **Buxbaum** JD, Daly MJ, Devlin B, Lehner T, Roeder K, State MW; Autism Sequencing Consortium. Neuron. 2012 Dec 20;76(6):1052-6.

Discussion papers:

Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with **autism**. Jamain S, Quach H, Betancur C, Råstam M, Colineaux C, Gillberg IC, Soderstrom H, Giros B, Leboyer M, Gillberg C, Bourgeron T; Paris **Autism** Research International Sibpair Study. Nat Genet. 2003 May;34(1):27-9.

SHANK1 Deletions in Males with Autism Spectrum Disorder. Sato D, …, Scherer SW. Am J Hum Genet. 2012 May 4;90(5):879-87.

May 8: shank autism genetics/group 5

Background reading:

The emerging role of **SHANK** genes in neuropsychiatric disorders. Guilmatre A, Huguet G, Delorme R, Bourgeron T. Dev Neurobiol. 2014 Feb;74(2):113-22.

Shank mutant mice as an animal model of **autism**. Yoo J, Bakes J, Bradley C, Collingridge GL, Kaang BK. Philos Trans R Soc Lond B Biol Sci. 2013 Dec 2;369(1633):20130143.

Discussion paper:

Sociability and motor functions in Shank1 mutant mice. Silverman JL, Turner SM, Barkan CL, Tolu SS, Saxena R, Hung AY, Sheng M, Crawley JN. Brain Res. 2011 Mar 22;1380:120-37.

Autism-associated mutations in ProSAP2/Shank3 impair synaptic transmission and neurexin-**neuroligin**-mediated transsynaptic signaling. Arons MH, Thynne CJ, Grabrucker AM, Li D, Schoen M, Cheyne JE, Boeckers TM, Montgomery JM, Garner CC. J Neurosci. 2012 Oct 24;32(43):14966-78.

May 15 Cntnap 2 in autism /group 6

Background review papers:

What does **CNTNAP2** reveal about autism spectrum disorder? Peñagarikano O, **Geschwind** DH. Trends Mol Med. 2012 Mar;18(3):156-63.

Discussion paper:

Recessive symptomatic focal epilepsy and mutant contactin-associated protein-like 2. **Strauss KA**, Puffenberger EG, Huentelman MJ, Gottlieb S, **Dobrin** SE, Parod JM, Stephan DA, Morton DH. N Engl J Med. 2006 Mar 30;354(13):1370-7.

Exogenous and evoked oxytocin restores social behavior in the **Cntnap2** mouse model of **autism**. Peñagarikano O, Lázaro MT, Lu XH, Gordon A, Dong H, Lam HA, Peles E, Maidment NT, Murphy NP, Yang XW, Golshani P, Geschwind DH. Sci Transl Med. 2015 Jan 21;7(271):271ra8.

May 22: Neuroligin autism genetics/group 7

Background reading:

Singh S.K. and Eroglu C. (2013). Neuroligins Provide Molecular Links between Syndromic and Non-Syndromic Autism. Sci. Signaling. Jul 9;6(283):re4.

Discussion paper:

Autism-related **neuroligin**-3 mutation alters social behavior and spatial learning. Jaramillo TC, Liu S, Pettersen A, Birnbaum SG, Powell CM. **Autism** Res. 2014 Apr;7(2):264-72.

Autism-associated **neuroligin**-3 mutations commonly impair striatal circuits to boost repetitive behaviors. **Rothwell** PE, Fuccillo MV, Maxeiner S, Hayton SJ, Gokce O, Lim BK, Fowler SC, Malenka RC, Südhof TC. Cell. 2014 Jul 3;158(1):198-212.

May 29: complex autism genetics/group 8

Background reading:

Behavioral profiles of mouse models for **autism** spectrum disorders. Ey E, Leblond CS, Bourgeron T. **Autism** Res. 2011 Feb;4(1):5-16. doi: 10.1002/aur.175.

Discussion paper:

Shared synaptic pathophysiology in syndromic and nonsyndromic rodent models of autism. Baudouin SJ, Gaudias J, Gerharz S, Hatstatt L, Zhou K, Punnakkal P, Tanaka KF, Spooren W, Hen R, De Zeeuw CI, Vogt K, **Scheiffele** P. Science. 2012 Oct 5;338(6103):128-32.

June 5 Other animal models for autism/group 9

Background reading:

The neurobiology of **autism**. Pardo CA, Eberhart CG. Brain Pathol. 2007 Oct;17(4):434-47. Review

Discussion paper:

Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, Codelli JA, Chow J, Reisman SE, Petrosino JF, Patterson PH, Mazmanian SK. Cell. 2013 Dec 19;155(7):1451-63.

Fmr1 and Nlgn3 knockout rats: novel tools for investigating **autism** spectrum disorders. Hamilton SM, Green JR, Veeraragavan S, Yuva L, McCoy A, Wu Y, Warren J, Little L, Ji D, Cui X, Weinstein E, Paylor R. Behav Neurosci. 2014 Apr;128(2):103-9.