Course name: Neurogenetics

3000 level course
Required: Introductory Biology I & II.
Meets 2x week

Course Description " Neurogenetics – How Genes Build our Brains"

This course provides an introduction to Neurogenetics. Neurogenetics explores the role of genetics in the development and function of the nervous system. The course will be focused on teaching classic and contemporary concepts in genetics and neuroscience, rather than cataloguing mere facts. The course will emphasize the discovery processes, historical figures involved in these processes and methodologies of discovery. The ultimate goal of this course is to gain an understanding of the underlying principles of how the nervous system of an animal differentiates and functions. A central organizational theme of the course is the presence of a common thread and narrative throughout the course, which comes in the form of an animal model system, the roundworm *Caenorhabditis elegans.* Research in *C. elegans* has served as a paradigm for how simple genetic model systems have informed our view on the genetics of nervous system development and function. Blocks of lectures on this animal model by the instructors will be followed by blocks of paper presentations by students that are focused on showing how lessons learned from simple invertebrate systems have applied to other more complex, vertebrate nervous systems.

The course is intended for neuroscience-inclined students (e.g. neuroscience majors) who want to learn about how genetic approaches have informed our understanding of brain development and function and, vice versa, for students with an interest in molecular biology and genetics, who want to learn about key problems in neuroscience and how genetic approaches can address them.

Besides a significant focus on scientific methodology, the discovery process conveyed in this course is further manifested by a reading of a historical narrative on the beginning days of neurogenetics, encapsulated in the book "*Time, Love, Memory: A Great Biologist and His Quest for the Origins of Behavior"* by Columbia Journalism Professor Jonathan Weiner. Professor Weiner will visit at the end of the course for a Q&A.

Reading:

1) Required reading: two books that describe specific aspects of the history of neuroscience & genetics:
   - *Rapport, R "Nerve Endings – The discovery of the synapse"*
   - *Weiner, J "Time, Love, Memory: A Great Biologist and His Quest for the Origins of Behavior"*
2) Papers for discussion (includes Background reading for Paper discussion)
3) Recommended Textbook for Background: "Development of the Nervous System" Sanes, Reh & Harris, 4th edition (2019)

Exams:

1) Midterm: One conceptual question, one question regarding history books
2) Final: Class content

Grading:

1) Exams (midterm and final; midterm will be weighted less than final)
2) Paper presentation
3) Take home questions after paper presentation
4) Class participation (during lecture & paper presentations)
5) Attendance (no more than 2 absences)

Course Schedule:

Fall 2023 (8:40am)	Topic
Wed Sept 6	*Lecture 1:* **History of problems, concepts and ideas in developmental neuroscience & developmental genetics**
Mo Sept 11	*Lecture 2:* **How to describe the brain: Maps of the nervous system**
Wed Sept 13	*Lecture 3:* **Genetic control of neuronal differentiation, part 1**
Mo Sept 18	*Lecture 4:* **Genetic control of neuronal differentiation, part 2**
Wed Sept 20	*Lecture 5:* **How neurons diversify into specific subclasses**
Mo Sept 25	*Paper presentation #1*
Wed Sept 27	*Paper presentation #2*
Mo Oct 2	*Lecture 6:* **How to build a brain: The Genetics of cell migration and axon pathfinding**
Wed Oct 4	*Paper presentation #3*
Mo Oct. 9	*holiday, no class; Oct 10: Course drop deadline*
Wed Oct 11	*Paper presentation #4*
Mo Oct 16	*Lecture 7:* **How the neurons talk to each other: The Genetics of synapse formation, structure and function**
Wed Oct 18	*Paper presentation #5*
week of Oct 23	MIDTERM EXAM
Mo Oct 30	*Lecture 8:* **Neuronal remodeling and plasticity**
Wed Nov 1	*Lecture 9:* **The (Neuro)genetic tool box: Mapping mutants and designing mutants**
Mo Nov 6	*holiday, no class*
Wed Nov 8	*Lecture 10:* **Genetics of Laterality: how the left and the right side of the brain are made to be different from one another**
Mo Nov 13	*Lecture 11:* **The Genetics of sleep**
Wed Nov 15	*Paper presentation #6*
Mo Nov 20	*TX giving week (no class)*
Wed Nov 22	*TX giving week (no class)*
Mo Nov 27	*Lecture 11:* **Genetic of sex & the brain, part 1**
Wed Nov 29	*Lecture 12:* **Genetic of sex & the brain, part 2**
Mo Dec 4	*Paper presentation #7*
Wed Dec 6	*Paper presentation #8*
Mo Dec 11	Q&A with Jonathan Weiner (Author of “Time, Love & Memory”) and Class wrap-up
Fr Dec 16th	FINAL EXAM

Detailed Syllabus:

History of problems, concepts and ideas in developmental neuroscience & developmental genetics

I will provide an overview of historical figures, problems and approaches in neuroscience and developmental genetics. I will start with Ramon y Cajal (Nobel Laureate 1906), the founder of the "neuron theory" who was the first to "visualize" – and synthesize into a coherent picture - structural components of the brain. I will discuss Hermann Muller (Nobel 1946) and George Beadle (Nobel 1958) who brought up the concept of mutational analysis to study biological processes. We will finish with the most influential "neurogeneticists" Sidney Brenner (Nobel 2002) and Seymour Benzer who pioneered the use of simple genetic model systems - C.elegans and Drosophila - to study nervous system development and function.

Further Reading:

These 2 books provide the early days of modern day neuroscience (Rapport book) and describe how to key figures, Brenner and Benzer, started the field of neurogenetics (Weiner books).

- *Rapport, R "Nerve Endings – The discovery of the synapse"*
- *Weiner, J "Time, Love, Memory: A Great Biologist and His Quest for the Origins of Behavior"*

How to describe the brain: Maps of the mature nervous system

To understand how any structure, any organisms or even just a single organ develops, one needs to have a description of its component parts. Hence, before getting into the genetics of neuronal development and function, I will first frame the problem by breaking down the brain into "parts lists", composed of molecules, cells and synaptic connections. I will make the point that while many efforts are underway in many different systems, there is only one nervous system for which we have a complete and comprehensive parts list – that of the nematode *Caenorhabditis elegans*. I will discuss anatomical maps, functional maps, gene expression maps in *C. elegans* (and describe the status of such map making in other organisms). I will use these maps to illustrate the unique feature of the nervous system – its astounding degree of distinct cell types, thereby posing the central question of this class: how is such cellular diversity generated during development; this will be the subject of next weeks class.

Further Reading

- Schafer, W (2016) "Nematode Nervous Systems", Current Biology 26, R937–R980

Genetic control of neuronal differentiation

These lectures will dive deeply into the classic genetic approaches that Sydney Brenner has taken to study the genetics of nervous system development. I will first describe the core concept of genetic screens – pioneered by George Beadle (Nobel Laureate 1958 for "one gene-one enzyme" hypothesis) – which uses a defined phenotype as a "read-out" for define genetic disruptions that affect this phenotype. I will describe how Brenner's original screens for mutants in which the animal does not behave properly identified selector genes that control the identity of individual neuronal cell types. Modern day screens that used different types of neuronal identity read-outs to reveal more selector genes will be covered as well. Similar selector genes have been identified in vertebrates and will be covered in ensuing paper presentations.

Further Reading

Hobert, O (2016) "Terminal selectors of neuronal identity", Curr. Top. Dev. Biol. 116:455-75
Underwood, E (2015) "The Brain's Identity Crisis", Science 349, 575-577
Masland, R (2004) "Neuronal cell types", Current Biology 14, 497-500

Poulin et al. (2016) “Disentangling neural cell diversity using single-cell transcriptomics” Nature Neuroscience 19, 1131-1141

How neurons diversify into specific subclasses

The key feature that sets a nervous system apart from any other organ is the enormous diversity of cell types contained within this organ. How can one make sense of the multitude of neuron types? Common organizational principles have emerged from examining properties of individual neuron types. One organizational feature of many nervous systems – again most clearly exemplified in the exceptionally well-characterized nervous system of *C. elegans* - is the existence of groups of neurons that share a set of common traits but that can be further divided into individual neuron types and subtypes. I will describe such classification and neuronal diversification schemes in C.elegans and will describe how genetic studies have revealed underlying principles of diversifying neuronal classes into subclasses.

Further Reading

Kerk et al. (2017) “Diversification of *C. elegans* motor neuron identity via selective effector gene repression” Neuron 93, 80–98

The (Neuro)genetic tool box: Mapping mutants and designing mutants

Before moving into “real world” problems of brain development and function, I will discuss key technologies for neurogenetic analys. I will describe how the molecular lesions in mutant animals, retrieved from unbiased mutant screens for neuronal phenotypes, are identified (“forward genetics”).

Further Reading

- Doitsidou, M et al. (2016) “Next-Generation Sequencing-Based Approaches for Mutation Mapping and Identification in Caenorhabditis elegans.”, Genetics. 2016 Oct;204(2):451-474
- Jorgensen, Em and Mango SE (2002) “The art and design of genetic screens: Caenorhabditis elegans” Nature Reviews Genetics volume 3, pages 356–369

How to build a brain: The Genetics of cell migration and axon pathfinding

How is the intricate architecture of a brain, characterized by precise positioning of neuronal cell bodies and guidance of their axons and dendrites to specific targets, genetically instructed? Here again, genetically amenable model organisms like *C.elegans* have made key contribution by identifying molecules through genetic mutant screens. One major focus will be the two best characterized patterning system, the Netrin/unc-6 system that operates throughout all animal nervous systems and which was first discovered in *C.elegans*.

Further Reading

- Hedgecock, E.M. et al. (1987) “Genetics of cell and axon migrations in Caenorhabditis elegans” Development 100 (3), 365-382
- Hedgecock, E.M. et al. (1990) The unc-5, unc-6, and unc-40 genes guide circumferential migrations of pioneer axons and mesodermal cells on the epidermis in C. elegans” Neuron 4(1), 61-85
- Colavita et al. (1998) “Pioneer axon guidance by UNC-129, a C. elegans TGF-beta” Science 281, 706-709
- Chisholm et al. (2016) “The Genetics of Axon Guidance and Axon Regeneration in Caenorhabditis elegans” Genetics 204, 849–882
- Ziel and Sherwood (2010) “Roles for Netrin Signaling Outside of Axon Guidance: A View from the Worm” Dev. Dyn., 1296–1305
- Sun et al., (2011) “Netrins: versatile extracellular cues with diverse functions” Development 138, 2153-2169

How neurons talk to each other: The Genetics of synapse formation, structure and function

The synapse is the critical information relay station of the nervous system. The complex cellular apparatus that define the functional properties of a synapse has been identified by a combination of classic biochemical approaches in vertebrates, but also by genetic screens in invertebrates. One key problem is how the position and placement of synapses – and synaptic partner choice – is genetically controlled and here again genetic approach have made important in inroads. One recurring theme in synapse formation is the reutilization of molecular cues that were earlier in cellular migration and axon outgrowth.

Further Reading:

- Ackermann et al. (2015) “Presynaptic active zones in invertebrates and vertebrates” EMBO reports Vol 16 | No 8 | 2015 923
- Cherra and Jin (2015) Advances in synapse formation:forging connections in the worm” WIREs Dev Biol, 4:85–97

Neuronal remodeling and plasticity

In this lecture, we will cover a key feature of any nervous sytem – its plasticity, i.e. its ability to modulate structural and functional features. Neuronal plasticity is evident in many different context, and includes remodeling events during development or repair or remodeling events in response to internal and external conditions. Using *C. elegans* again as a model we will learn that pheromonal cues can trigger an extensive remodeling of its nervous system, altering structural features and behavioral paradigms. I will discuss the genetic mechanisms that underlie this plasticity. One key component of this system is an insulin/IGF1 signaling system that works not only in *C.elegans* but also in vertebrate system to control neuronal plasticity. I will also discuss optogenetic tools that allow us to genetically manipulate neuronal activity.

Further Reading

- Costandi, M (2016) “Neuroplasticity” The MIT Press Essential Knowledge Series
- Fielenbach and Antebi “C. elegans dauer formation and the molecular basis of plasticity” Genes Dev. 2008 Aug 15;22(16):2149-65.
- Yaniv & Schuldiner O “A fly's view of neuronal remodeling” Wiley Interdiscip Rev Dev Biol. 2016 Sep;5(5):618-35.

The Genetics of Sleep

Sleep is characterized by altered patterns of brain activity. I will discuss here how specific neurons in the brain regulate overall activity patterns of the brain, essentially putting the brain (and the entire organism) to sleep. One important class of molecules in this process are neuropeptides, small peptides secreted from specific “sleep neurons”, acting on multiple distinct target neurons throughout the brain.

Further Reading

- Trojanowski & Raizen (2016) “Call it Worm Sleep” Trends in Neuroscience 39(2) 54
- Bringmann (2018) “Sleep-Active Neurons: Conserved Motors of Sleep”, Genetics 08(4):1279-1289

The Genetics of Sex & the brain

Male and female brains are different. As simple model systems have told us, male and female brains, they display sexual dimorphisms on the level of function, anatomy, circuitry and gene expression. We will discuss these differences in detail and discuss mechanisms for how these differences genetically programmed? The lecture will be focused again on C.elegans, while later paper presentations will discuss sexual dimorphisms and courtship behavior in Drosophila and mice and venture in specific aspects of sex-specific behavior (male aggression behavior).

Further Reading:

- Yamamoto, D. & Koganezawa, M. “Genes and circuits of courtship behaviour in Drosophila males”. Nature Rev. Neurosci. 14, 681–692 (2013).
- Anderson (2016) “Circuit modules linking internal states and social behaviour in flies and mice”, Nature Rev. Neurosci. 17, 692-704
- McCarthy & Arnold (2011) “Reframing sexual differentiation of the brain” Nature Neuroscience 14, 677-683
- Yang & Shah (2014) “Representing Sex in the Brain, One Module at a Time” Neuron 82, 261-78

How the left and the right side of the brain are made to be different from one another

After their generation, neurons are not irreversibly locked into a specific shape, form or function. In this and the ensuing lectures, I will discuss how genes act to in specific cellular contexts to transform neuronal identity, and hence brain structure and function. In this lecture I will discuss neuronal laterality, a fundamental problem in neuroscience. Despite their gross morphological symmetry, animal nervous systems can perceive and process information in a left/right asymmetric manner. How left/ right asymmetric functional features develop in the context of a bilaterally symmetric structure is a very poorly understood problem, in part because very few morphological or molecular correlates of functional asymmetries have been identified so far in vertebrate or invertebrate nervous systems. One of the very few systems in which a molecular correlate for functional lateralization has been uncovered is the sensory system of *C. elegans*. I will discuss the genetic specification mechanisms involved in generating these left-right asymmetries. In this lecture, I will also introduce an important neurogenetic tools – genetically encoded sensors for neuronal activity that allow us to visualize brain activity (lateralized brain activity in this case).

Further Reading

- Sun & Walsh (2006) “Molecular approaches to brain asymmetry and handedness” Nature Reviews Neuroscience 7, 655-662
- Hobert, O (2014) " Development of left/right asymmetry in the *Caenorhabditis elegans* nervous system: From zygote to postmitotic neuron" *genesis* 52:528–543