SCRB 182

Got (new) Brain?
The Evolution of Brain Regeneration

Fall 2016
Capped at 22 students

Course Head:

Paola Arlotta, Ph.D.
Professor of Stem Cell and Regenerative Biology
Fairchild 358C
7 Divinity Avenue
Cambridge, MA 02138
Phone: 617 496 9810
paola_arlotta@harvard.edu

Course Time:

DAYS: Mondays and Wednesdays
TIME: 2:30-4PM
LOCATION: Sherman Fairchild building 268

Office hours:

Paola Arlotta Mondays 4-5:00PM
Giorgia Quadrato Tuesday 11AM-noon
Ryoji Amamoto Thursday 2-3:00PM

Teaching Staff:

Giorgia Quadrato, Ph.D
Department of Stem Cell and Regenerative Biology
Harvard University
7 Divinity Avenue
Cambridge, MA 02138
giorgiaquadrato@fas.harvard.edu

Ryoji Amamoto, B.S.
Department of Stem Cell and Regenerative Biology
Harvard University
7 Divinity Avenue
Cambridge, MA 02138
ramamoto@gmail.com

Contact with questions on course syllabus, course site, attendance and material.

Course Grading

30% - Class participation: attendance, class discussions, and lab participation
25% - Midterm Exam I
25% - Midterm Exam II
20% - Final research project and presentation

Prerequisites: Life and Physical Sciences A or Life Sciences 1a; Life Sciences 1b; MCB 80 or equivalent Introduction to Neuroscience course (or permission of the instructor).

Suggested Readings: *Selected chapters* from:
1. Developmental Biology (10th Edition) by Scott Gilbert
2. Principles of Neural Science (5th Edition) by Eric Kandel, James Schwartz, and Tom Jessell
(Both books reserved at Harvard Libraries)
Selected Review articles (available on course website)
Selected primary articles (available on course website)

Description:
Why can planarians regenerate their brain and we can't? Is an immutable brain the price to pay to be human? This course will cover concepts and theories on the evolutionary changes in the capacities by different organisms to regenerate their nervous system. Material will be taught in a dynamic setting that combines lectures and brainstorming of the literature with hands-on experience in the laboratory. Students will become familiar with classic, paradigm-changing experiments that have shaped the way we think about brain regeneration and repair and also consider the newest theories on cellular reprogramming as a way to regenerate the nervous system. Material covered in class will be used as a starting point to consider, contrast and evaluate how regenerative capacities have changed during evolution and to brainstorm paths forward towards new solutions for brain regeneration in species, like humans, that have not mastered this art. Emphasis will be placed on allowing students to creatively think about key scientific questions and to "feel" the excitement of scientific discovery in this fast changing field.

Date	**Topic**
Wed 8/31:	**Making a new brain? The "raise and fall" of dogmas about brain regeneration**. *Introductory lecture*
Mon 9/5:	**Labor Day (NO CLASS)**
Wed 9/7:	**Craziness in biology. The evolution of extreme regenerative strategies for survival.** *Lecture:* We will cover and discuss informative strategies used by different organisms to regenerate tissues and organs and consider their trade-offs for organ function and survival of the organism. *Suggested Readings:*

Schmich, J., Kraus, Y., De Vito, D., Graziussi, D., Boero, F., and Piraino, S. (2007). Induction of reverse development in two marine Hydrozoans. The International journal of developmental biology *51*, 45-56.

Gurdon, J.B. (1962). The developmental capacity of nuclei taken from intestinal epithelium cells of feeding tadpoles. Journal of embryology and experimental morphology *10*, 622-640.

Mon 9/12: **From stem cells to tissues and back again: Reprogramming strategies to make new neurons.**

Lecture: We will consider the capacity of different cell types to reprogram their identity and make new neurons.

Suggested Readings:

Rouaux, C., and Arlotta, P. (2013). Direct lineage reprogramming of post-mitotic callosal neurons into corticofugal neurons in vivo. Nature cell biology *15*, 214-221.

Caiazzo, M., Dell'Anno, M.T., Dvoretskova, E., Lazarevic, D., Taverna, S., Leo, D., Sotnikova, T.D., Menegon, A., Roncaglia, P., Colciago, G.*, et al.* (2011). Direct generation of functional dopaminergic neurons from mouse and human fibroblasts. Nature *476*, 224-227.

Wed 9/14 **Guest Lecture: Evolution of regeneration in invertebrates.**
Prof. Mansi Srivastava (Harvard University)

Suggested Readings:

Adler, C.E., and Sánchez Alvarado, A. (2015). Types or States? Cellular Dynamics and Regenerative Potential. Trends in cell biology *25*, 687-696.

Wagner, D.E., Wang, I.E., and Reddien, P.W. (2011). Clonogenic neoblasts are pluripotent adult stem cells that underlie planarian regeneration. Science (New York, NY) *332*, 811-816.

Mon 9/19

Regenerative landscape through evolution.
Lecture: We will discuss the "mystery" of why different species have distinct regenerative responses. Not just a matter of complexity.

Brainstorming: This class will entail a brainstorming session to collectively consider aspects of nervous system regeneration and why some species can regenerate while others can't.

Suggested Readings:

Bely, A.E., and Nyberg, K.G. (2010). Evolution of animal regeneration: re-emergence of a field. Trends in ecology & evolution *25*, 161-170.

Wed 9/21

Tissue regeneration in planaria: can "memory" be regenerated?
Brainstorming: This class will entail a brainstorming session to collectively consider aspects of nervous system regeneration in planaria and the ability to perhaps regenerate previously encoded "memories".

Lecture: Development and evolution of the vertebrate brain Part 1. We will cover the main events and some of the mechanisms that shape the development of progressively more complex nervous systems.

Suggested Readings:

Shomrat, T., and Levin, M. (2013). An automated training paradigm reveals long-term memory in planarians and its persistence through head regeneration. The Journal of experimental biology *216*, 3799-3810

Dasen, J.S., Tice, B.C., Brenner-Morton, S., and Jessell, T.M. (2005). A Hox regulatory network establishes motor neuron pool identity and target-muscle connectivity. Cell *123*, 477-491.

Mon 9/26

Laboratory Ia: Regeneration in invertebrates.
Laboratory: In this hands-on laboratory class, students will have an opportunity to run their own experiments designed to test the regenerative capacities of regenerative, invertebrate model organisms.

Wed 9/28:

Development and evolution of the vertebrate brain. Part 2.
Lecture: We will cover the main events and some of the mechanisms that shape the development of progressively more complex nervous systems.

Suggested Readings:

Lodato, S., and Arlotta, P. (2015). Generating neuronal diversity in the mammalian cerebral cortex. Annual review of cell and developmental biology *31*, 699-720.

Taverna, E., Götz, M., and Huttner, W.B. (2014). The cell biology of neurogenesis: toward an understanding of the development and evolution of the neocortex. Annual review of cell and developmental biology *30*, 465-502.

Mon 10/3:

Neurogenesis and axon growth.
Lecture: we will cover key experiments that shed light on the capacity that organisms have to make new neurons and to wire into new circuits in response to stimuli like injury.

Suggested Readings:

Bond, A.M., Ming, G.-L.L., and Song, H. (2015). Adult Mammalian Neural Stem Cells and Neurogenesis: Five Decades Later. Cell stem cell *17*, 385-395.

David, S., and Aguayo, A.J. (1981). Axonal elongation into peripheral nervous system "bridges" after central nervous system injury in adult rats. Science (New York, NY) *214*, 931-933.

Bei, F., Lee, H.H., Liu, X., Gunner, G., Jin, H., Ma, L., Wang, C., Hou, L., Hensch, T.K., Frank, E.*, et al.* (2016). Restoration of Visual Function by Enhancing Conduction in Regenerated Axons. Cell *164*, 219-232.

Wed 10/5:

Rewiring the brain. Is it even possible?
Brainstorming : this class will be dedicated to brainstorming ideas on ways to change brain wiring and/or affect the birth of new neurons in adult organisms.
45 minutes will be dedicated to review and practice exam material.

Mon 10/10	**Columbus Day (NO CLASS)**
Wed 10/12	**Midterm Exam I**
Mon 10/17	**Laboratory Ib (analysis): Regeneration in invertebrates.** We will analyze the results of experiments performed in laboratory Ia. This will include (but is not limited to) imaging and analysis of the results, troubleshooting of experimental design, and use of data to model the process of regeneration.
Wed 10/19	**Brain regeneration in vertebrates: a tale of salamanders and mice.** *Lecture:* we will cover concepts of nervous system regeneration in vertebrates endowed with prominent capacities to regenerate multiple organs (i.e. axolotls). *Suggested Readings:* Tanaka, E.M. (2016). The Molecular and Cellular Choreography of Appendage Regeneration. Cell 165, 1598-1608. Amamoto, R., Huerta, V.G., Takahashi, E., Dai, G., Grant, A.K., Fu, Z., and Arlotta, P. (2016). Adult axolotls can regenerate original neuronal diversity in response to brain injury. eLife 5.
Mon 10/24	**Laboratory IIa: Regeneration in vertebrates** *Laboratory*: In this hands-on laboratory class, students will have an opportunity to run their own experiments to test the regenerative capacities of vertebrates, using salamanders (axolotls) and mice as model systems.
Wed 10/26	**Plasticity of neurons and circuits as a form of functional repair.** *Lecture:* We will consider and contrast the capacity of young and adult brains to change local circuit and synapses and evaluate this in the context of functional brain repair. *Suggested Readings:* Hensch, T.K. (2005). Critical period plasticity in local cortical circuits. Nature reviews Neuroscience *6*, 877-888.

Pizzorusso, T., Medini, P., Berardi, N., Chierzi, S., Fawcett, J.W., and Maffei, L. (2002). Reactivation of ocular dominance plasticity in the adult visual cortex. Science (New York, NY) *298*, 1248-1251.

Mon 10/31

Brain machine interfaces: plasticity at work

Lecture: We will consider the capacity of the brain to move mechanical devices and the underlying cellular and circuit level mechanisms.

Brainstorming: This class will include a 45 minutes brainstorming component to allow students and instructors to consider application of these methods to brain repair.

Suggested Readings:

Nicolelis, M.A., and Lebedev, M.A. (2009). Principles of neural ensemble physiology underlying the operation of brain-machine interfaces. Nature reviews Neuroscience *10*, 530-540.

Donati, A.R.C., Shokur, S., Morya, E., Campos, D.S.F., Moioli, R.C., Gitti, C.M., Augusto, P.B., Tripodi, S., Pires, C.G., Pereira, G.A.*, et al.* (2016). Long-Term Training with a Brain-Machine Interface-Based Gait Protocol Induces Partial Neurological Recovery in Paraplegic Patients. Scientific Reports *6*, 30383.

Wed 11/2

Human neurodegenerative and neuropsychiatric disease: what happens to the brain and why can't we fix it?

Lecture: We will cover molecular, cellular and structural changes associated with prominent human neurodegenerative and psychiatric diseases and brainstorm potential solutions to regain brain function.

Suggested Readings:

McCarroll, S.A., and Hyman, S.E. (2013). Progress in the genetics of polygenic brain disorders: significant new challenges for neurobiology. Neuron *80*, 578-587.

Mei, Y., Monteiro, P., Zhou, Y., Kim, J.-A.A., Gao, X., Fu, Z., and Feng, G. (2016). Adult restoration of Shank3 expression rescues selective autistic-like phenotypes. Nature *530*, 481-484.

Sztainberg, Y., Chen, H.-m.M., Swann, J.W., Hao, S., Tang, B., Wu, Z., Tang, J., Wan, Y.-W.W., Liu, Z., Rigo, F.*, et al.* (2015). Reversal of phenotypes in MECP2 duplication mice using genetic rescue or antisense oligonucleotides. Nature *528*, 123-126.

Mon 11/7 **<u>Guest Lecture:</u> Professor Steven McCarroll**

<u>Suggested Readings:</u>

Sekar, A., Bialas, A.R., de Rivera, H., Davis, A., Hammond, T.R., Kamitaki, N., Tooley, K., Presumey, J., Baum, M., Van Doren, V.*, et al.* (2016). Schizophrenia risk from complex variation of complement component 4. Nature.

Macosko, E.Z., Basu, A., Satija, R., Nemesh, J., Shekhar, K., Goldman, M., Tirosh, I., Bialas, A.R., Kamitaki, N., Martersteck, E.M.*, et al.* (2015). Highly Parallel Genome-wide Expression Profiling of Individual Cells Using Nanoliter Droplets. Cell *161*, 1202-1214.

Wed 11/9 **Making a new brain in the dish: Stem cell-derived cerebral organoids.**

<u>Lecture:</u> We will explore the latest technologies and experimental approaches used to generate complex brain tissue from pluripotent stem cells and application to understand human development, regeneration and disease in the dish.

<u>Suggested Readings:</u>

Lancaster, M.A., Renner, M., Martin, C.-A.A., Wenzel, D., Bicknell, L.S., Hurles, M.E., Homfray, T., Penninger, J.M., Jackson, A.P., and Knoblich, J.A. (2013). Cerebral organoids model human brain development and microcephaly. Nature *501*, 373-379.

Kelava, I., and Lancaster, M.A. (2016). Stem Cell Models of Human Brain Development. Cell stem cell *18*, 736-748.

Mon 11/14 : **Brainstorming of all materials covered: review and practice exam material.**

Wed 11/16 **Midterm Exam II**

Mon 11/21	**Laboratory IIb (analysis): Regeneration in vertebrates** We will analyze the results of experiments performed in laboratory IIa. This will include analysis of the data, examination of distinct regenerative outcomes, brainstorming of underlying mechanisms and of implications for brain function.
Wed 11/23	**Thanksgiving Holiday (NO CLASS)**
Mon 11/28	**Final Assignment** Students will work in small groups to conceive present a research project that addresses questions related to brain regeneration.
Wed 11/30:	**Final Assignment** Students will work in small groups to conceive present a research project that addresses questions related to brain regeneration.