SCRB 180: Development, Plasticity, and Regeneration in the Mammalian Brain
Fall 2024

Description: *Why do neuronal axon extensions within nerves of limbs regenerate after traumatic or combat injuries, but analogous axon tracts in the spinal cord and brain do not, e.g. in spinal cord injury? Why do diseases often have mutations in every cell of the body, and in every neuron type of the brain, but only 1 or 2 neuron types out of thousands degenerate or fail, e.g. in ALS or Parkinson's disease? Why and how does often remarkable recovery from brain surgery or injury occur in young children, but not so much in later life? How is the brain set up to sense the world, integrate incoming sensory information, and lead to movement and behavior, and how is that organized during development? Might we overcome lack of spinal cord regeneration? Might we reverse or repair neuron degeneration in ALS, e.g.? How might advanced brain-computer interface prosthetic devices add value? What's up with stem cell biology– including hope, hype, and reality? To address these questions, we motivate ourselves by disease and what it might take to develop therapeutics, then study initial development, then study blocks to regeneration and the remarkable work-arounds of "plasticity", then integrate these toward future solutions.*

We will highly interactively study regenerative biology of the mammalian central nervous system (CNS), motivated by a focused and related set of human CNS disorders: This course will discuss molecular and cellular mechanisms of regeneration and repair in the mammalian central nervous system (CNS), motivated by prototypical examples in the motor control systems and circuitry of the cerebral cortex and spinal cord centrally relevant to spinal cord injury, ALS / Lou Gehrig's disease ("amyotrophic lateral sclerosis", and related disorders), and spinal muscular atrophy (SMA). We will take an approach integrating developmental and regenerative biology: we will compare and contrast aspects of embryonic neural development (molecular and cellular) with adult neural plasticity; discuss limitations to neuronal and axonal regeneration in the mature mammalian CNS following degeneration or injury; examine CNS regeneration approaches directed at overcoming intrinsic limitations; explore developmental molecular controls, gene manipulation, and cellular reprogramming to promote neurogenesis (birth of new neurons), axonal regeneration, and directed differentiation of progenitors and stem cells in diseased adult mammalian brain; and consider technology such as "brain-computer interfaces". This course has always functioned as an interactive seminar rather than a lecture course, and includes the trajectory of knowledge and thinking over the past century, plus the state-of-the-art in these fields, emphasising the need for a healthy measure of skepticism in some fields. Sections cover advanced experimental approaches, critical reading of the literature, and conceptual thinking.

Instructor: Jeffrey D. Macklis, Max and Anne Wien Professor of Life Sciences
Department of Stem Cell and Regenerative Biology, and Center for Brain Science
Bauer Laboratories, Room 103, 7 Divinity Avenue
(617) 495-5413; jeffrey_macklis@harvard.edu

Macklis Office Hours: TBA for ease globally. Core times: Tuesdays, Thursdays 12:45-1:20 PM (open), 2:50-3:30 PM (open), and by appointment

Teaching Fellows: Dustin Tillman (dtillman@g.harvard.edu), Ph.D. student, Molecules, Cells, and Organisms (MCO) program; and Mariale Vicent Allende (maria_vicentallende@hms.harvard.edu), M.D.-Ph.D. student, HMS-HST and Program in Neuroscience (PiN)

TF Office Hours: TBA for ease globally

Course time: *Tuesdays and Thursdays 1:30-2:45 PM* (attendance is essential for the course format)
Section w/ TFs: TBA; Default is Tues OR Thurs 2:55-3:55 PM (same TF Tu/Th each wk)

Course Grading:	Contribution, Discussion, and Section Presentations	25%
	Essay and Problem Set homework (approx 2-4)	10%
	Midterm Exam 1	20%
	Midterm Exam 2	20%
	Final “Blue Sky” Group and Individual Project	25%

Prerequisites: Life and Physical Sciences A or LS 1a/LS 1b or LS 50A/B; MCB 80 or equivalent “Introduction to Neuroscience” course or SCRB 50 or MCB 60, or permission of the instructor

Policies regarding student collaboration

I. Collaboration on Weekly Reading, Analysis, Interpretation, Joint Presentations, and Joint Phase of Final Projects Permitted & Encouraged

a. Reading, Analysis, and Joint Phase of Final Project Assignments
Discussion and the exchange of ideas are essential to academic work. For reading, analysis, interpretation, and the joint-phase of final project written and presentation assignments in this course, you are encouraged to consult with your classmates on the choice of extra reading topics, final project topics, and to share sources. You may find it useful to discuss your chosen topics and areas of interest with your peers, particularly if you are working on the same topics as a classmate. However, you should ensure that any written work you submit for evaluation for the independent phase of the final projects is the result of your own research and writing, and that it reflects your own approach to the topic. You must also adhere to standard citation practices in this discipline and properly cite any books, articles, websites, lectures, etc. that have helped you with your work. If you received any help with your writing (feedback on drafts, etc.), you must also acknowledge this assistance (even if from fellow students).

b. Section Paper and Topical Presentations
Discussion and the exchange of ideas are essential to doing academic work. For section assignments in this course, you are encouraged to consult with your classmates as you work on your published paper and related topical presentations. However, after discussions with peers, make sure that you have fully read, and can interpret and present the assigned paper and its related topic yourself, and ensure that the slides and any related work, oral or written, that you submit for evaluation are the result of your own efforts. In addition, you must cite any books, articles, websites, lectures, etc. that have helped you with your work using appropriate citation practices. Similarly, you must list the names of students with whom you have collaborated on the presentations.

II. Collaboration Prohibited on Exams (two self-administered, take-home 75 min midterms)

Students should be aware that in this course collaboration of any sort on any exams submitted for formal evaluation is not permitted. Since our goal is to stress concepts and integration of information, relevant background factual information will, in general, be provided in the exam questions themselves, to avoid the need for simple memorization. This means that exams will be "closed book" and that you may not discuss your exam questions, ideas, exam answers, or any other aspects of the exams with other students. All work should be entirely your own. If you build on work of others that you read in preparation, you must use simple-but-appropriate citation practices to acknowledge the direct use of books, articles, websites, lectures, discussions, etc., that you have intellectually built upon to complete your answers.

III. Artificial intelligence (AI) software and systems are becoming part of our world, and I allow their use in proper circumstances. That said, it is against Harvard University policy, and much more broadly in the academic world and society, of course, to falsely claim work product of AI as your own. Further, AI systems often simply generate false material when they cannot locate a correct answer. Even more central to this seminar, your work is meant to be your own very focused take on the material and specific issues we are discussing in a unique and integrative way. AI systems do not have a very good “judgement” system– they tend to exhaustively acquire and integrate, without the knowledge of the subtle focus and balance you wish to bring to an assignment (one can direct AI to some extent in these regards via optimal prompts, but not in a fully human way). *Thus, if you wish to experiment with AI, go ahead, then write your own answers/papers assessing the AI “take” vs. your own likely slightly or vastly different take. Treat the AI system as a a discussant with you, if you choose to employ it. And, state explicitly that you did*.

Harvard Guide to Using Sources (https://usingsources.fas.harvard.edu/)

Harvard Handbook for Students (https://handbook.college.harvard.edu/)

Session **Date** **Topic** (*these exact session descriptions are tentative, and will be modestly revised*)

Week One

optimally, viewing prior to first session (*re-assigned between sessions 1 & 2 if not watched in advance*):
integrated examples of motor skills video
full Richard Olney ALS video
full Tom's Story ALS video (except end; optional)
Travis Roy 11 Seconds video

1 9/3 (Tues) Intro to the course: course overview, goals, organization, format, and concept of student final project teams

Framing the Problem: Two patients (by video) with the neurodegenerative disease ALS illustrate and motivate interactively outlining the underlying neurobiology, relevant cortical and spinal cord (SC) circuitry/neuroanatomy of the motor control system, the challenges, and routes to regeneration and repair. Problem-based motivation and partial / modified Socratic approach: developmental and regenerative biology centrally relevant to the prototypical problems of spinal cord injury, ALS / motor neuron diseases.

Travis Roy's spinal cord injury (SCI) in his first NCAA game (by video) further motivates interactively defining and outlining the cellular anatomy, circuitry, systems of relevant developmental neurobiology, and mechanistic options toward spinal cord regeneration and repair.

Brief outline of relevant brain and spinal cord circuitry; neuron and other cell populations as regeneration and repair targets

assigned viewing for the next session (*first four if not watched prior to session 1*):
integrated examples of motor skills video
full Richard Olney ALS video
full Tom's Story ALS video (except end; optional)
Travis Roy 11 Seconds video

additional: Spinal muscular atrophy (SMA) introduction and excerpts of patient videos

assigned reading for next session:
"Neurons and Glia", Bear, Chapter 2
"Structure of the CNS", Bear, Chapter 7, p. 168-173

section 3:50-4:45 PM "drop in" Section with both TFs and Prof. Macklis to raise student questions, discuss some initial background for students with diverse educational foundations; others might choose to use the time for part of assigned reading.

2 9/5 (Thurs) Corticospinal and sensory anatomy and neurobiology; spinal cord circuitry and cell populations (neuronal and glial); populations central to SCI injury, ALS degeneration, and repair

Add spinal motor neurons and disease to corticospinal anatomy and neurobiology; relevant spinal cord circuitry and cell populations (neuronal and glial) – the "lower motor neurons" of ALS, SMA

assigned reading for next session:
"Differentiation and survival of nerve cells" Kandel, Chapter 53
"Neuronal specification in the spinal cord" Jessell, *Nat Rev Genetics*, 2000

Week Two

3 9/10 (Tues) Developmental spinal cord neurogenesis

Subtype-specific neuronal development: spinal motor neurons (SMN)

Inter-relations between SMN development, diversity, and SMA / ALS degeneration, cellular mechanistic and therapeutic modeling / screening, and regeneration

assigned reading for next session:
"Specification of cortical projection neurons: transcriptional mechanisms" Ozkan et al., 2020
"Molecular logic of neocortical projection neuron specification and development" Greig*, Woodworth*, *Nat Rev Neurosci*, 2013 (Optional reading)
"Motor cortex connections" Sahni et al, 2020 (Optional advanced reading)

section Paper discussions:
"Neuronal specification in the spinal cord" Jessell, *Nat Rev Genetics*, 2000
"Directed differentiation of embryonic stem cells into motor neurons" Wichterle, *Cell*, 2002

4 9/12 (Thurs) Developmental brain neurogenesis I

Subtype-specific CNS neuronal development: cerebral cortex projection neurons; focus on corticospinal motor neurons (CSMN) – the "upper motor neurons" of ALS (and related motor neuron diseases HSPs and PLS)

assigned reading for next session:
"The growth and guidance of axons" Kandel, Chapter 54
"The trip of the tip: understanding the growth cone machinery" Lowery and Van Vactor, *Nat. Rev. Cell Biol.* 2009

Week Three

5 9/17 (Tues) Developmental cerebral cortex neuronal subtype development II
Development of axons and circuitry formation I
a. CNS axon guidance mechanisms during development
b. General, SMN, PNS
c. Corticospinal axon guidance

assigned reading for next session:
"Central nervous system regeneration inhibitors and their intracellular substrates" Nash, *Mol Neurobiol*, 2009
"Identification and characterization of a bovine neurite growth inhibitor (bNI-220)" Spillman, *JBC*, 1998
"Prior exposure to neurotrophins blocks inhibition of axonal regeneration by MAG and myelin via a cAMP-dependent mechanism" Cai, *Neuron*, 1999
"Regeneration of dorsal column fibers into and beyond the lesion site following adult spinal cord injury" Neumann*, Neuron*, 1999
"Assembly of a new growth cone after axotomy: the precursor to axon regeneration" Bradke, *Nat. Rev. Neurosci.,* 2012
"Newt sequencing may set back efforts to regrow human limbs" Cormier, *Nature*, 2013 [commentary]

section Paper discussions:
"Neuronal subtype-specific genes that control corticospinal motor neuron development in vivo" Arlotta, *Neuron*, 2005
"*Ctip1* Controls Acquisition of Sensory Area Identity and Establishment of Sensory Input Fields in the Developing Neocortex" Greig*, Woodworth", *Neuron*, 2016

Experimental approaches discussion:
- Analysis of neural circuits using hodological tracers
- Isolation of cellular subtypes using FACS
- High throughput gene expression analysis approaches

6 9/19 (Thurs) Development of axons and circuitry formation II
a. CNS axon guidance mechanisms during development
b. General, SMN, PNS
c. Corticospinal axon guidance

assigned reading for next session:
"Central nervous system regeneration inhibitors and their intracellular substrates" Nash, *Mol Neurobiol*, 2009
"Identification and characterization of a bovine neurite growth inhibitor (bNI-220)" Spillman, *JBC*, 1998
"Prior exposure to neurotrophins blocks inhibition of axonal regeneration by MAG and myelin via a cAMP-dependent mechanism" Cai, *Neuron*, 1999
"Regeneration of dorsal column fibers into and beyond the lesion site following adult spinal cord injury" Neumann*, Neuron*, 1999
"Assembly of a new growth cone after axotomy: the precursor to axon regeneration" Bradke, *Nat. Rev. Neurosci.,* 2012
"Newt sequencing may set back efforts to regrow human limbs" Cormier, *Nature*, 2013 [commentary]

Week Four

7 9/24 (Tues) Development of axons and circuitry formation III
a. CNS axon guidance mechanisms in development; subcellular growth cone biology
b. Corticospinal axon guidance; subcellular growth cone biology

assigned reading for next session:
"Rewiring a Damaged Spinal Cord" Gravotta, *Scientific American*, 2013 [commentary]
"Spinal cord repair strategies: why do they work?" Bradbury, *Nat Rev Neurosci*, 2006

section Paper discussion:
"Chemotropic Responses of Retinal Growth Cones Mediated by Rapid Local Protein Synthesis and Degradation", Campbell, *Neuron*, 2001
"RNA transport and local translation in neurodevelopmental and neurodegenerative disease", Fernandopulle, *Nat Neurosci*, 2021
"Assembly of a new growth cone after axotomy: the precursor to axon regeneration", *Nat Rev Neurosci*, 2012, Bradke

Experimental approaches discussion:
- Live imaging of cells
- Recombinant fusion proteins
- *In vitro* axon guidance assays

8 9/26 (Thurs) Visit by Jisoo Kim (Harvard College '22, Quincy House; Harvard Medical School '27)
From Wheelchair to Bench and Back. Refining the biology of spinal cord injury and repair. Refining attainable and potentially transformative goals of regenerative biology.

SCI anatomical, cellular, and inflammatory pathology, mechanisms, and goals for regeneration

CSMN, SMN, oligodendroglia, glial scar introduction

assigned reading for next session:
"Glial inhibition of CNS axon regeneration" Yiu, *Nat Rev Neurosci*, 2006
"Electrical Stimulation of Spared Corticospinal Axons Augments Connections with Ipsilateral Spinal Motor Circuits after Injury" Brus-Ramer, *J Neurosci,* 2007
"Chronic Electrical Stimulation of the Intact Corticospinal System after Injury Restores Skilled Locomotor Control and Promotes Spinal Axon Outgrowth" Carmel, *J Neurosci,* 2010
"PTEN deletion enhances the regenerative ability of adult corticospinal neurons" Liu, *Nat Neurosci*, 2010

Week Five

9 10/1 (Tues) Inhibition of axons / regeneration after developmental circuitry formation – inhibitors and mechanisms
a. targets for molecular therapeutics
b. blocking antibodies, among other approaches
c. Growth factor delivery
d. Removal of inhibitory signals

assigned viewing for next session:
"*Sight of Mind*" "*London Taxi Drivers*" http://www.chedd-angier.com/frontiers/season11.html (Season 11, episode 1)

assigned reading for next session:
"Experience and the refinement of synaptic connections" Kandel, Chapter 56

section Paper discussion:
"Sustained axon regeneration induced by the co-deletion of PTEN and SOCS3" Sun, *Nature*, 2011
"A motor cortex circuit for motor planning and movement" Li, *Nature*, 2015

Experimental approaches discussion:
- Electrophysiology: Recording the activity of neurons
- Optogenetics: Manipulating the activity of neurons
- Fluorescent proteins

10 10/6 (Thurs) Structural, cellular and functional responses of the CNS to injury: organizational and functional plasticity I
a. redundant connectivity in the "mature" CNS
b. functional "re-wiring" based on use and disuse

assigned viewing for next session:
"Click vision X 2" https://www.youtube.com/watch?v=fnH7AIwhpik
(More detailed background, explanations): http://www.benunderwood.com/
Daniel Kish: http://www.cnn.com/2011/11/09/tech/innovation/daniel-kish-poptech-echolocation/
"Half Brain: "http://www.chedd-angier.com/frontiers/season11.html

assigned reading for next session:
"Repairing the damaged brain" Kandel, Chapter 57
"Extensive spontaneous plasticity of corticospinal projections after primate spinal cord injury" Rosenzweig, *Nat Neurosci,* 2010

Week Six

11 10/8 (Tues) Organizational and functional plasticity II
a. developmental variability of human plasticity
b. synesthesia – "crossed" sensation in humans and its lessons for CNS plasticity, regeneration, and repair

assigned reading for next session:
"Spinal Cord Repair in Adult Paraplegic Rats: Partial Restoration of Hind Limb Function" Cheng, *Science*, 1996
"Functional regeneration of respiratory pathways after spinal cord injury" Alilain, *Nature*, 2011

section Paper discussion:
"Spinal Cord Repair in Adult Paraplegic Rats: Partial Restoration of Hind Limb Function" Cheng, *Science*, 1996

Experimental approaches discussion:
- Transgenic mice as neuroscience tools
- Gene manipulation using viral infection
- Novel tools for gene manipulation

12 10/10 (Thurs) Cellular and molecular mechanisms to overcome limitations on axon regeneration in the mature CNS I – cellular and extracellular matrix "bridges"

assigned reading for next session:
"Chondroitinase ABC treatment opens a window of opportunity for task-specific rehabilitation" Garcia-Alias, *Nat Neurosci*, 2009

Week Seven

13 10/15 (Tues) Cellular and molecular mechanisms to overcome limitations on axon regeneration in the mature CNS II – alternative "bridges" and molecular, enzymatic approaches

section Paper discussion:
"Nerve regeneration restores supraspinal control of bladder function after complete spinal cord injury" Lee, *J Neurosci,* 2013

Experimental approaches discussion:
- Mouse models of spinal cord injury to study repair
- *In vivo* extracellular recordings to analyze neural circuits
- Microscopy for long-range projection neurons

14 10/17 (Thurs) Integration and Synthesis of first half of term; take-home Midterm Exam I

assigned reading for next session:
"Creating permissive microenvironments for transplantation into the CNS" Kim, *Trends in Biotechnology*, 2012
"Remodeling Myelin" Cossins, *The Scientist*, 2013 [commentary]

Week Eight

15 10/22 (Tues) Cellular replacement strategies I – overview
a. Transplantation but not circuit replacement
b. Neural transplantation
c. Progenitors, precursors, "stem cell" transplantation
d. Differentiation vs. paracrine effects of transplanted cell

assigned reading for next session:
"Long distance growth and connectivity of neural stem cells after severe spinal cord injury" Lu, *Cell*, 2012

section Paper discussion:
"Inhibitory Neuron Transplantation into Adult Visual Cortex Creates a New Critical Period that Rescues Impaired Vision" Davis, *Neuron,* 2015

Experimental approaches discussion:
- *In vivo* activity imaging using calcium indicators
- Neuronal microtransplantation

16 10/24 (Thurs) Cellular replacement strategies II
a. Transplantation and circuits

assigned reading for next session:
"Adult neurogenesis and neural precursors, progenitors, and stem cells in the adult central nervous system" *Textbook of Neural Repair and Rehabilitation*, Chapter 20, 2nd
"Adult neurogenesis in the mammalian brain: significant answers and significant questions" Ming, *Neuron*, 2011

Week Nine

17 10/29 (Tues) Progenitors, precursors, and stem cells in the adult CNS

Neurogenesis in the adult CNS I
a. Neurogenic niches in the adult brain
b. Constitutive adult neurogenesis

assigned reading for next session:
"Induction of neurogenesis in the neocortex of adult mice" Magavi, *Nature*, 2000
"Targeted neuronal death affects neuronal replacement and vocal behavior in adult songbirds" Scharff, *Neuron*, 2000
"Neuronal replacement from endogenous precursors in the adult brain after stroke" Arvidsson, *Nat Med*, 2002

section Paper discussions:
"Transplanted hypothalamic neurons restore leptin signaling and ameliorate obesity in db/db mice" Czupryn, *Science*, 2011
"Developmentally primed cortical neurons maintain fidelity of differentiation and establish appropriate functional connectivity after transplantation" Wuttke, *Nat Neurosci*, 2018
"Reprogramming to recover youthful epigenetic information and restore vision", Lu, *Nature*, 2020

Experimental approaches discussion:
- Ultrastructural analysis of neurons
- Cellular microtransplantation approaches

18 10/31 (Thurs) Neurogenesis in the adult CNS II
a. Induced adult neurogenesis

assigned reading for next session:
"Cerebral organoids model human brain development and microcephaly" Lancaster, *Nature*, 2013
"Induced neuronal cells: how to make and define a neuron" Yang, *Cell Stem Cell*, 2011
"Direct conversion of fibroblasts to functional neurons by defined factors" Vierbuchen, *Nature*, 2010
"3D Brain Organoids: Studying Brain Development and Disease Outside the Embryo" Velasco, *Annu Rev Neurosci*, 2020
"The rise of three-dimensional human brain cultures" Pasca, *Nature*, 2018

Week Ten

19 11/5 (Tues) Reprogramming, directed differentiation of pluripotent cells (ES; PS)

Reprogramming of adult cell types in the nervous system: potential therapeutic relevance and application

assigned reading for next session:
"*Fezf2* directs the differentiation of corticofugal neurons from striatal progenitors in vivo" Rouaux, *Nat Neurosci*, 2010
"*In vivo* reprogramming of circuit connectivity in postmitotic neocortical neurons" De la Rossa, *Nat Neurosci*, 2013
"Restoration of auditory evoked responses by human ES-cell-derived otic progenitors" Chen, *Nature*, 2012

section Paper discussion:
"Dynamics of hippocampal neurogenesis in adult humans" Spalding, *Cell*, 2013
"Adult neurogenesis in mammals", Gage, *Science*, 2019

Experimental approaches discussion:
- Subcellular fractionation
- Nucleic acid purification
- Principles of mass spectrometry

20 11/7 (Thurs) Reprogramming II (directed differentiation): adult progenitor "directed differentiation" using developmental controls
Integration and Synthesis II:
- toward axonal/circuit regeneration
- toward cellular replacement and models
- other directions? Technology? Brain-computer interfaces?

assigned reading for next session:
"Principles of neural ensemble physiology underlying the operation of brain-machine interfaces" Nicolelis, *Nat Rev Neurosci*, 2009 [selection to be updated]
"Monkeys Accept Virtual Arms as Own" Akst, *The Scientist*, 2013 [commentary]
"Restoration of upper limb movement via artificial corticospinal and musculospinal connections in monkey with spinal cord injury" Nishimura, *Front Neur Circuit*, 2013
"A cortical-spinal prosthesis for targeted limb movement in paralysed primate avatars", Shanechi, *Nat Comm*, 2014

Week Eleven

21 11/12 (Tues) [tentative] Guest Lecture: Miguel Nicolelis, Duke University
a. Brain-computer interfaces
b. Robotic solutions

assigned reading for next session:
Reread anything above that you might have skimmed or missed.

section Paper discussion:
"Rapid single-step induction of functional neurons from human pluriopotent stem cells" Zhang, *Neuron*, 2013

Experimental approaches discussion:
- Cell culture approaches
- Protein expression analysis
- Stem cells and cellular reprogramming

22 11/14 (Thurs) Project discussions, feedback, and whole class "brainstorming"

Integration and Synthesis III

assigned reading for next session:
Re-read anything above that you might have skimmed or missed.

Week Twelve

23 11/19 (Tues) Future prospects for application of developmental neuroscience to neural repair; team presentations of novel regenerative ideas and directions; group development of multi-aim programs toward final individual project proposals of one of the aims (Thursday and following Tuesday)

Project proposal talks I

24 11/21 (Thurs) Future prospects for application of developmental neuroscience to neural repair; team presentations of novel regenerative ideas and directions; group development of multi-aim programs toward final individual project proposals of one of the aims (Tuesday and prior Thursday)

Project proposal talks II

section Discussion of project ideas, obstacles, and refinements

Week Thirteen

25 11/26 (Tues) Half session Q&A, integration of approaches, mechanisms, directions I

Integration and Synthesis III

11/28 (Thurs) Thanksgiving – no class

section NONE

Week Fourteen

26 12/3 (Tues) Half session Q&A, integration of approaches, mechanisms, directions II

Integration and Synthesis IV; take-home Midterm exam II

Closing activity

Week Fifteen

12/13 (Fri) [tentative; due date to be assigned by Registrar] Final project papers due