MOLECULAR BIOLOGY OF THE BRAIN
BIOL SCI 448: M, W, 8:00 am – 9:40 am; BIOS 244
WINTER 2011

Instructor: Michael Chen, Ph.D.
Office: BIOS 235

Office hours: Mon, Wed, 10:00am -Noon;
Tues, Thurs, 10:00-11:00 am.
e-mail:
mchen@calstatela.edu

General Course Objectives: To understand the current concepts of and experimental approaches to the molecular biology of the cells of the nervous system.

Prerequisites: Biology 380 (Cell Biology), Biology 340 (Genetics)

Textbook:
Elements of Molecular Neurobiology. Smith, C.U., Wiley, 2002.

Original Scientific Literature: There will be 5 articles, which I have chosen from the scientific literature and which you are to summarize, and which are due on the dates indicated below. Summaries should be 2-3 double-spaced typed pages. Late summaries will be deducted 1 point for every weekday they are late.

LECTURES: I will lecture using almost exclusively PowerPoint slides. These lectures are available on my faculty webpage at: www.calstatela.edu/faculty/mchen

Course Schedule:			Book Chapters
Mon	1/3	General Introduction to the Course Molecular Biological Techniques – A Primer	Slides
Wed	1/5	Molecular Biological Techniques – A Primer (cont'd)	Slides
Mon	1/10	Flies and Mice as model systems	pp. 247-248; pp. 487-491
Wed	1/12	Gene expression: from precursor to mature neuron **Form groups (3-4) by this date**	Ch. 3, 4
Mon	1/17	MLK Holiday - University Closed	
Wed	1/19	Protein trafficking in neurons **Groups decide on topic by this date**	Ch. 15
Mon	1/24	Ion channels and electrical activity	Ch. 10, 11
Wed	1/26	Molecular biology of neurotransmitter release	Ch. 15, 16

Mon	1/31	**Midterm Exam 1** ***SNARE* article summary due**	
Wed	2/2	Molecular biology of postsynaptic structures	Ch. 17
Mon	2/7	Signal reception: Ligand gated-ion channel receptors ***PSD-95b* article due** **Presentation titles/first two references due**	Ch. 10
Wed	2/9	Signal reception: G protein-coupled receptors	Ch. 8
Mon	2/14	Synapse-to-nucleus calcium signaling ***GPCR Assembly* article due**	Ch. 8, 10, 17
Wed	2/16	**Midterm Exam 2**	
Mon	2/21	Signalling by tyr phosphorylation in the nervous system **Presentation outlines and full bibliography of references due**	Slides
Wed	2/23	Mature neurons: Signal transduction – ser/thr kinases	Slides
Mon	2/28	The cytoskeleton ***Src/ERK/CREB* article summary due**	Ch. 15
Wed	3/2	Neuronal plasticity	Ch. 20
Mon	3/7	Genetic basis of human neuronal diseases, aging and death of neurons. ***GSK Memory* article summary due**	Ch. 21
Wed	3/9	**Final Examination** (Final exam during regular class period)	
Mon	3/14	**Journal Review Presentations/Poster Session 8:00 – 10:30 am** (during scheduled final exam period)	

As instructor, I reserve the right to slightly alter the above topic schedule as time permits.

Grading:

2 Midterm exams	100 points each
Attendance	2 points/class period = 28 points
Journal article summaries	10 points each = 50 points.
J. Review presentation	100 points
Presentation participation	25 points
Final Exam	100 points
	~ 500 points total

I do not grade on a curve and generally, the bottom and top 3% of a range (e.g., 80-90%) will get "-" and "+" grades, respectively.

****I don't accept assignments via e-mail, except under dire circumstances.****

Academic Honesty: Students are expected to read and abide by the University's Academic Honesty Policy, which can be found at www.calstatela.edu/academic/senate/handbook/ch5a.htm. Students who violate this policy will be subject to disciplinary action, and may receive a failing grade in the course for a single violation.

Tests: The tests will be a combination of short answer, multiple choice, and perhaps some matching. The final exam will not be comprehensive. No make-up tests will be scheduled. With an excused (*i.e*. discussed in advance or doctor's note) absence for the midterm, the value of the final exam will be increased to compensate for the missed test. If evidence of emergency can be provided for a missed final, an Incomplete will be given until the final exam the following summer quarter.

Only ***your*** medical emergency or illness will excuse you from an exam. Medical emergencies of relatives, friends, relatives of friends, friends of relatives, weddings, anniversaries, parties, *etc*. are not valid reasons for missing an exam. Nor are they valid reasons for asking me to allow you to take an exam during a time other than the scheduled time.

Attendance: To help ensure that people attend the lectures, I take attendance (2 points/class period) by passing around a "sign-in" sheet. You ***must*** print you name on this sheet ***during*** class; please do not come up to me at some later time after class to tell me that you were not absent, but did not place your name on the sheet because you forgot, arrived late, *etc*. I do not have a photographic memory and will not remember if you indeed were really present.

Journal Review Project: The sequencing of the human genome ~ 10 years ago heralded in a new area for molecular biology of every organ system. Thus, molecular neurobiology has become one of the most active and growing fields in the life sciences. I have included, as a required project for this class, the review of one specific area of neurobiology research with specific emphasis on the molecular aspects (the general subjects are listed below). The review will be summarized in a power-point presentation during the final exam period. Three to five relevant research papers from the *primary* literature will be used in your review. Book chapters and review articles should also be used in your preparation, but do not count toward the 3-5 research papers (you should have about 8 items total in your bibliography). In addition to text (described below), your presentation should include some form of visual aids (such as bullet points/lists, figures from research studies or figures explaining experimental methods), in order to make your presentation clear.

The format of your presentation should include:

Introduction (2-4 slides)

Significance of this research area
Historical background
Hypothesis (or group of related hypotheses) tested in the chosen recent studies

Review of example research studies and key results (4-6 slides)

Purpose of each experiment
Method(s) used
Results obtained
Interpretation of the results (Do they support or refute the hypothesis? What is their significance in light of other studies?)

Conclusions (1-2 slides)

Summarize the advances in this area of research that you have presented, and state their importance to medicine or the understanding of how the nervous system functions.

One important aspect of this exercise will be developing the ability to summarize material in a succinct manner, so that the audience can learn a few key points. Presentations will be prepared and delivered by a team of 3-4 students. At professional meetings/conferences, presentations are limited to 10-12 minutes. **Thus, your presentation can take no longer than 10-12 minutes. If it goes over, I will have to cut you off.**

Grading:
Presentations will be graded on these points:

- Clarity
- Evidence of understanding
- Efficiency of words, lists or tables
- Quality of visual aids

Your title and a list of 2 of your references will be due at the beginning of week 6 (due at the beginning of lecture 2/7/11).

Your full bibliography of 3-5 research papers (plus supporting review papers or books) and a two-page outline of your presentation will be due at the beginning of week 8 (due at the beginning of lecture on 2/21/11).

Peer Evaluations:

You will also be required to evaluate the presentations of your peers both within your own group and the presentations of other groups. Your within-group evaluations will go toward your peers' grade as 20% of the presentation grade (25/125). This is to help make sure that everyone contributes equally.
Your evaluation of other presentations will not be used for your or their final grade, but I will use these as a credit/no-credit basis and could be used to tip the balance of a grade in

the event of a borderline final presentation grade. Briefly evaluate each poster and presentation on these points:

Introduction – What is the purpose of the studies presented? Is there a testable scientific hypothesis stated? Does the presenter clearly state the significance of the studies in relation to recent scientific knowledge?

Review of studies and results – Is it possible to understand the procedures used in the experiments, and are specialized or technical terms well-defined?

Conclusions – What is the "take home" message? Has the presenter demonstrated an understanding of the significance of the results (in terms of their contribution to science or medicine)?

A**ll peer evaluations will be kept confidential.**

General Topics: (Students will sign up for a topic and presentation group during the second week)

Possible topics:
See the course schedule (above) for possibilities.

Specific Objectives – Student Learning Outcomes:

Students will be able to expatiate on the following:

- Protein Trafficking in Neurons:
  - Regulated transport to the trans golgi network
  - Morphology
  - Development of polarity
    - Synapse formation
    - Axonal development
  - Polarity in mature neurons
  - Polarity signals
    - Dendrites
    - Axons

  Postsynaptic targeting
    - mRNA targeting
    - Protein targeting via lipid rafts

  Specific transport proteins and pathways
    - $GABA_A$ receptors
    - NMDA receptors
    - AMPA receptors

  Postsynaptic removal of receptors
    - Mechanism and pathways available
    - Receptor endocytosis

- Lateral diffusion

❖ Ion Channels and Electrical Activity
- The voltage sensor of ion channels
- Voltage-gated Na^+ channels
- Voltage-gated K^+ channels
  - Molecular characterization of kv channels
  - *Xenopus* oocytes as a heterologous expression system for studying cloned ion channels
  - K^+ selectivity if kv channels
  - Inactivation mechanisms of kv channels
  - Functional role and modulation of *Shaker*-like K^+ channels
- Inward rectifying K^+ channels and cell excitability
- Voltage-gated Ca^{2+} channels

❖ Molecular Biology of Neurotransmitter Release
- Modern concepts in neurotransmitter release: synaptic vesicle
- Aspects of neurotransmission
- Vesicle storage and mobilization
- The synapsin family of phosphoproteins
- Vesicle docking
- Vesicle fusion
- Membrane retrieval and neurotransmitter loading

Learning and synapses
- The neuronal software
- Functional synaptic plasticity
- Morphological synaptic plasticity

❖ Molecular Biology of Postsynaptic Structures
- Structural features and components of the excitatory PSD
- Plasma membrane proteins
- Signaling proteins
- Cytoskeletal proteins
- Linker proteins
- Functional interactions between PSD components
- Proposed functions of the PSD
- The PSD in synaptic plasticity
- PSD structure and pathophysiology of the CNS
  - Cerebral ischemia
  - Experimental models of impaired LTP and learning tasks
  - Streptozotocin-diabetic rats

❖ Signal recepton: Ligand-gated ion channel receptors:
- The receptor molecules
- Molecular diversity and its control
- Genes and gene expression
- Alternative splicing

- RNA editing
- Translational control
- Post-translational modification
- Receptor assembly and trafficking
- 3D structure and the molecular basis of receptor properties
- nAch receptor group structure

❖ Signal reception: G protein-coupled receptors

The G protein-coupled receptor (GPCR) superfamily
The receptor-G-protein cycle
Types of G proteins and their second messenger pathways
Non G-protein-mediated pathways
Overall structural features: Rhodopsin family, Glucagon-like family, mGluR/$GABA_B$ family
Receptor-ligand interactions
Receptor-G protein interactions:
How are receptor-G protein interactions measured?
Structural features of receptors involved in G protein activation
Cell-type specific factors
Regulation of G protein-coupled receptor function
Desensitization/resensitization
Receptor trafficking
Mechanisms of long-term down regulation
Regulation at the level of the G protein

❖ Synapse-to-Nucleus Calcium Signaling

- Ca^{2+} as an intracellular 2^{nd} messenger
- Synaptic plasticity in the nervous system
  Control of gene expression
  Ca^{2+}-responsive DNA regulatory elements and their transcription factors
- The physiological importance of CREB
  The mechanism of CREB activation
  The role of CREB binding protein (CBP) in CREB-mediated transcription
- Decoding the Ca^{2+} signal

❖ Signalling by tyrosine Phosphorylation in the Nervous System

- Receptor tyr kinases
- Mechanisms of activation and signaling of receptor tyr kinases
- Non-receptor tyr kinases
- Tyr phosphatases
- Role of protein tyr phosphorylation during development of the nervous system
- Role of tyr phosphorylation in the regulation of ion channels and receptors
- Role if protein tyr phosphorylation in synaptic plasticity

- Other roles of protein tyr phosphorylation in the normal and diseased nervous system

❖ Mature Neurons: Signal transduction-ser/thr kinases

- 2^{nd}-messenger-dependent ser/thr protein kinases
  - Ca^{2+}-CAM kinase
  - PKC
- 2^{nd}-messenger-independent protein kinases
  - MAPK

Neuronal substrates of kinases

Neurotransmitter release

Ligand-gated ion channel and K^+ channels

Transcription factors

The role of the kinases in synaptic transmission and cross-talk between the different kinase pathways

The role of the kinases in synaptic plasticity: PKA, CaMKII, PKC, MAPKs

Ser thr phosphatases: calcineurin and protein phosphatase I

❖ Cytoskeleton

Components of the neuronal cytoskeleton: microtubules, microfilaments, intermediate filaments

Interaction of cytoskeletal components

The cytoskeleton in neuronal morphogenesis

Axonal maturation

Neuronal polarity

The cytoskeleton in neuronal plasticity

The cytoskeleton in intraneuronal transport

Axonal and dendritic transport

Slow axonal transport

Fast axonal transport

Molecular motors

The cytoskeleton in neurodegenerative diseases

Alzheimer's

Amyotrophic lateral sclerosis

Charcot-Marie-Tooth disease type 2

❖ Neuronal Plasticity

Experimental models of neuronal plasticity

Hippocampal LTP

Limbic system kindling

Temporal phases of synaptic plasticity

Ca^{2+} as the trigger

Rapid, transient plasticity

Slower, sustained plasticity

Transcription factor families

Induction of transcription factors

Induction of other immediate-early genes

Induction of late-response genes

Relationship between early and late responses

- Genetic Basis of Human Neuronal Diseases
  The molecular basis of various neuronal diseases, such as Alzheimer's, Parkinson's, Motor Neuron Disease (ALS), and mood disorders will be explored.
- Aging and Death of Neurons: Various mechanisms of how neurons age and the determinants of their death will be examined.