Module 1: Gene Expression

Course Faculty
Instructor: Alex Gann
Invited Experts: Adrian Krainer, Christopher Vakoc

Tutor: Jonathan Cahn

Lecture 1: Gann
- Early ideas and bacterial models

Lecture 2: Gann
- Understanding a regulatory network

Lecture 3: Gann
- Eukaryotic networks and development

Lecture 4: Krainer
- Splicing mechanisms and regulation

Lecture 5: Vakoc
- Emerging concepts and mechanisms of transcriptional control

Student Evaluation:
- Problem Set 40%, Discussions 40%, Class Participation 20%

Learning Objectives
- Transcriptional activation and repression
- Cooperativity and specificity in gene regulation
- Signal integration and combinatorial control
- Regulation by RNAs
- Splicing and processing of RNAs
- Histone and DNA Modification

Learning Outcomes
- Explain how genes are turned on and off
- Explain how specificity of gene regulation is achieved
- Discuss establishment vs. maintenance of gene expression

Reference Material
Textbooks:
- Watson, J.D. *et al.*, *Molecular Biology of the Gene*, 2013, Chapters 13, 14, 18, 19, 20

Reviews:

Problem Set Papers:
Discussion 1: Gann


Discussion 2: Krainer

Module 2: Gene Regulatory Logic and the Construction of Multicellular Organisms: Insights from humans, flies, and worms

Course Faculty
Lead Instructor: Christopher Hammell
Tutor: Peipei Wu

Lecture 1: Hammell
- Cell fate specification and the construction of a basic organ
- Overview of how intracellular and extracellular signaling define an array of distinct cell fates using the C. elegans vulva as a model.
- Integrate these general principles of intra- and extracellular signaling in the context of disease.

Lecture 2: Hammell
- Control of temporal gene expression
- Overview of C. elegans development and the utility of having a hard-wired developmental program verses the spatially-defined one discussed in last lecture.
- C. elegans heterochronic pathway and the emergent themes that are common to all metazoans.
- Comparison of temporal gene expression strategies: developmental timers, circadian timers, and biological oscillators that construct repeated, spatial elements in development.

Lecture 3: Hammell
- Control to size and death during development
- Overview of forms of animal/plant growth.
- Insights from single cells and model organism.

Lecture 4: Hammell
- Germline formation
- Overview of forms of animal/plant growth.
- Examples from model organisms and the genetic analysis of the problem.
- Cell autonomous and non-autonomous regulatory networks and how to find them genetically.

Student Evaluation:
- 50% participation in daily discussions during lectures
- 50% based on paper discussions

Learning Objectives
- To understand the fundamentals of recurrent Gene Regulatory Networks (GRN) that orchestrate various types of cell fate specification.
- To understand what makes a good “model system” for developmental biology.
- To define what a stem cell is and how they operate in embryogenesis, post-embryonic development, tissue regeneration and the germ line.
- To understand what the limitations of studying developmental biology from a genetic perspective and to determine what are the solutions to this problem.
- Integrate large-scale gene expression studies to understand the coordination of gene expression during development.
- Gain a practical understanding of how cell death, developmental timing, cell and organ growth control, germline...
development and tissue regeneration contribute to normal developmental processes.

Learning Outcomes
- Elaborate on an understanding of a functional model system for a particular developmental problem
- Design tractable methods to investigate developmental problems.
- Critically access modern literature focused on developmental biology.
- Gain a fundamental understanding of how high-volume genomic approaches contribute to our understanding of gene expression trajectories and progression of developmental processes.

Reference Material
Textbooks:

Reviews:


Problem Set Papers:

Discussion 1 Papers:

Discussion 2 Papers:
Module 3: The Brain: genes, circuits, and behavior

Course Faculty
Organizer: Jessica Tollkuhn

Lecture 1: Tollkuhn
Behavior
• Neuroethology, innate behavior
• Sex-differences in the brain and behavior: hard-wired or plastic?
• Assessing validity of rodent models of psychiatric disease
• Rodent behavior assays

Lecture 2: Tollkuhn
Circuits
• Overview of neural circuit approaches:
  Circuit mapping, genetic and viral methods, imaging neural activity, optogenetics, chemogenetics.

Lecture 3: Tollkuhn
Genes
• Activity-dependent gene expression
• Methodologies for studying gene regulation
• DNA methylation, MeCp2, Rett Syndrome
• Neuroepigenetics: searching for causality
• Transgenerational inheritance: facts and controversies


Lecture 4: Tollkuhn
Neurodevelopment and Cell Identity
• Cortical patterning
• Neuronal migration, “inside-out” corticogenesis
• Neural Cell Types, insights from single-cell sequencing
• Critical periods, development of the visual system

Discussion 1: Tollkuhn “Validity of rodent disease models”

Discussion 2: Tollkuhn “Discussion of mystery paper”

Problem Set Paper
Mystery paper! Students will write the title and abstract for the preprint.

Student Evaluation:
• Problem Set 40%, Discussions 40%, Class Participation 20%
Learning Objectives
Gain proficiency in the following:
- Activity-dependent gene expression
- DNA methylation and chromatin organization in neurons
- Epigenetic gene regulation in neurons
- Ocular dominance columns and ocular dominance shift
- Critical periods for visual system and brain sexual differentiation
- Innate behaviors: fear, aggression, parenting, pair-bonding
- Sex differences in the brain and behavior
- Common rodent behavior paradigms and what they measure
- Rodent models of autism, schizophrenia, depression, anxiety
- Morphogens and transcription factor gradients in neurodevelopment
- Corticogenesis: excitatory and inhibitory neurons
- The importance of single-cell sequencing for neuroscience

Learning Outcomes
- Students will gain proficiency in reading and discussing papers outside of their expertise
- Discuss common pitfalls in experimental design and interpretation of neuroepigenetic studies
- Demonstrate an understanding of critical periods in brain development
- Be familiar with common rodent models of human psychiatric conditions
- Discuss how neural activity leads to changes in gene expression
- Discuss how hormones organize and activate innate behavior circuitry
- Demonstrate an understanding of epigenomic and single-cell approaches in neuroscience

Lecture #1 Reference Material

Lecture #2 Reference Material

Lecture #3 Reference Material

Lecture #4 Reference Material
Course Faculty
Organizer: Leemor Joshua-Tor
Module Tutor: Ankur Garg (garg@cshl.edu)

Lecture 1: Joshua-Tor
• Basic principles

Lecture 2: Garg
• Pymol Tutorial

Lecture 3: Joshua-Tor
• A structural perspective of RNA interference

Lecture 4: Joshua-Tor
• X-ray crystallography

Lecture 5: Joshua-Tor
• CryoEM and other methods in structural biology

Student Evaluation:
Presentation and written portion of protein tales: 60%
Lecture participation: 20%
Problem Set: 20%

Learning Outcomes
• Understand the principles of RNA interference pathways
• Demonstrate understanding of protein and nucleic acid structure and their utility in understanding biology
• Have the ability to download structures, visualize and interrogate them.
• Demonstrate understanding of protein-nucleic acid and protein-protein interactions
• Design methods to distinguish between direct and indirect protein interactions
• Discuss strategies for obtaining macromolecular structure and learn to decide which approach to use and what information one can obtain from each method
• Learn how to read structural biology papers and critically assess them

Reference Material
Textbooks:
• Watson, J.D. et al., Molecular Biology of the Gene, 2013
• Liljas, et al., Textbook on Structural Biology
• Rupp, Biomolecular Crystallography
• McPherson, Introduction to Macromolecular Crystallography

Reviews:

**Discussion 1: Protein Tales**
Module 5: Study Section

Course Faculty
Instructor: Linda Van Aelst

Session 1: Van Aelst
- Module Overview
- The NIH Grant System
- Grants Distribution

Session 2: Van Aelst
- Study Section I

Session 3: Van Aelst
- Study Section II

Session 4: Van Aelst
- Study Section III

Student Evaluation:
- Primary reviewer presentation 40%, Written review 30%, Secondary reviewer presentation 20%, Class Participation 10%

In the Study Section Module, you will read and critique grants, much as an NIH Study Section reviewing applications would do (although we will have much more time per grant for presentation and discussion). We have pre-selected real grants for review. Every student is expected to read every grant and participate in the discussion of every grant. In addition to this, each student will be assigned as PRIMARY on one grant as SECONDARY on another grant and as a READER on a third grant.

PRIMARY reviewers will: (A) Prepare a 30 minute-presentation to serve as the basis of discussion of the grant. 15 minutes will be on the scientific Background and to introduce Specific Aims (Background presentation). 15 minutes will be devoted to summarize Preliminary Results and to evaluate the Experimental Design (Grant presentation) and 5 minutes will be devoted to the PI, environment, etc. (B) Each primary reviewer will also prepare a written critique of the grant, along the lines of the NIH Center for Scientific Review guide (http://www.csr.nih.gov/guidelines/R01.htm).

SECONDARY reviewers will read the grant in detail and in advance of the meeting. They should prepare specific commentary and questions and will have ~ 10 minutes to present them before the general discussion period.

READERS will read the grant in detail and in advance of the meeting. They should prepare specific questions for the general discussion period.

Written Critiques
The written critiques do not have to provide introductory information. They should begin by summarizing the overall goal of the proposed research in context with the importance of the questions to be addressed within the field of proposed study. The strengths and weaknesses of each approach should be outlined, with an aim-by-aim critique being generally the easiest to present and understand. Alternative and perhaps better ways to approach each question should be presented if they exist. In exemplary cases, it would be good to postulate why such approaches might not have been proposed. The review should finish with a brief discussion of the P.I. and their qualifications, the environment in which the research is to be performed and the appropriateness of the available facilities and budget/personnel. Any concerns about
regulatory issues with vertebrate animals, human subjects, data sharing and human embryonic stem cell research should be noted. An overall score should then be suggested based on the standard NIH priority score rating scale.

The oral presentations for the primary referee should proceed similarly except that they should include an introduction to the field and the work proposed. This should be sufficient to bring a non-expert up to speed with the topic of the grant. Secondary referees should follow the primary referee with comments and concerns on the science proposed and other areas (P.I. etc.) outlined above. The reader will not be responsible for a formal presentation but is expected to support the discussion.

Learning Objectives
• Gain an understanding of the structure and practices of an NIH study section
• Gain an understanding of the scored criteria of an NIH R01 grant
• Learn to write a written grant review
• Learn to present a grant as the Primary and Secondary Reviewer

Learning Outcomes
• Demonstrate an understanding of the structure and practices of an NIH study section
• Provide an oral and written critique of an NIH R01 grant
• Contribute to the critical analysis of an NIH R01 grant as a Group

Reference Material
• There are a number of sources to assist you in this assignment. The NIH has produced a video of a mock study section. “Inside the NIH Grant Review Process”, is a 39-minute video developed by the NIH Center for Scientific Review. The video includes excerpts from the reviews of 3 types of NIH applications: R01 - Research project grant, K08 - Mentored clinical scientist career development grant and R03 - Small research grant.

- This video (or transcript of the video) can be viewed at http://www.csr.nih.gov/Video/Video.asp. Companion materials to the study section include the grant applications and summary statements used in the discussions. The summary statements, often referred to as “pink-sheets” because they used to be sent on pink copy paper, are the written critiques prepared by the study section, similar to this assignment.

- An annotated research grant is available from the NIH’s National Institute of Allergy and Infectious Disease http://www.niaid.nih.gov/ncn/grants/app/default.htm.

- You might also find the list of guidelines for a study section chair useful. These can be found at http://www.csr.nih.gov/events/guidelineschairs.htm.

- Some terms you may come across (from the Center for Scientific Review):
  Percentile: represents the relative position or rank of each priority score (along a 100.0 percentile band) among the scores assigned by a particular study section.
  Priority score: A numerical rating that reflects the scientific merit of the proposed research relative to the "state of the science."
  Study section: panel of experts established according to scientific disciplines or current research areas for the primary purpose of evaluating the scientific and technical merit of grant applications. Also called scientific review groups (SRGs).
  Summary statement: a combination of the reviewers' written comments and the SRA's summary of the members' discussion during the study section meeting. It includes the recommendations of the study section, a recommended budget, and administrative notes of special consideration.