# MCB197 | Gene Regulation: A Bench-to-Bedside Journey

Spring 2024

Tuesdays & Thursdays, 3:00 - 4:15 PM
Room location: Harvard Hall 201

**Instructors**

Dr. Amanda Whipple
Assistant Professor
Department of Molecular and Cellular Biology

Dr. Michele Markstein
Curriculum and Pedagogy Manager
Department of Molecular and Cellular Biology

For any administrative questions related to this course, including questions intended for Dr. Whipple, email mmarkstein@g.harvard.edu!

**Teaching Fellows**

Rishabh Kapoor
Graduate Student
rkapoor@g.harvard.edu

Aditi Limaye
MD-PhD Student
alimaye@hms.harvard.edu

Serafina Nieves
Graduate Student
snieves@g.harvard.edu

**Drop-in hours**

| When | Where | Teaching Staff |
|---|---|---|
| Monday, 3 - 4 PM | Biolabs Rm 2062/2064 | Rishabh Kapoor |
| Tuesday, 5 - 6 PM | Biolabs Rm 1087 | Aditi Limaye |
| Wednesday, 2:30 - 3:30 PM | Biolabs Rm 1033 | Serafina Nieves |
| Friday, 3 - 4 PM | Zoom [Link] | Michele Markstein |

**Website:** https://canvas.harvard.edu/courses/132995

**This course syllabus is subject to change*

**Course Description**

How do all our cells carry the same DNA yet perform distinct functions in our body? How do cells know what type of proteins they should produce? These questions are answered by studying gene regulation. In this class, you will look at the rules and mechanisms that enable a subset of genes to be selectively expressed in each cell. You will examine how disruptions in gene regulation contribute to disease and you will learn how to design therapeutic strategies for correcting gene expression in disease. This course adopts a "bench-to-bedside" approach, mirroring the translation of basic scientific research in the laboratory into practical medical applications in the clinic. Take advantage of this unique opportunity to explore advances in gene regulation, from its molecular foundation to practical implementation in gene therapy.

This course is recommended for students with broad scientific interests, including research and medicine, and desiring an advanced course in molecular and cellular biology.

*Prerequisites: Life and Physical Sciences A or Life Sciences 1a; Life Sciences 1b*

**Course Overview**

Each week you'll engage in complementary classroom sessions — "bench" and "bedside" — that bridge the gap between scientific foundations and practical applications.

*Bench Sessions*

Topics covered will include genome architecture, gene expression, RNA processing, and the non-coding genome.

- **Didactic Lectures:** Engage in lectures that explore historical discoveries and modern methodologies in gene regulation.
- **Interactive Discussions:** Foster critical thinking through in-class discussions that encourage dissecting complex scientific concepts, sharing insights, and debating hypotheses.
- **Primary Research Analysis:** Analyze and critique primary research publications, identifying key experiments and open questions.

*Bedside Sessions*

Topics covered will include genome browser, gene therapies (CRISPR, ASO), and scientific illustration.

- **Practical Application - Genomics:** Learn to visualize and analyze genome features and patterns of gene expression using human genomic and transcriptomic data available through public genome browsers (no coding involved).
- **Practical Application - Therapeutics:** Apply knowledge of gene regulation and gene therapies to correct the molecular basis of disease.

As a capstone project, you will draw upon insights acquired from bench and bedside sessions to design a practical therapeutic strategy for a genetic condition of your choice, which will then be presented to the class in a scientific poster session.

**Schedule At-A-Glance**

| WK | TUE | BENCH SESSIONS | THR | BEDSIDE SESSIONS |
|---|---|---|---|---|
| 1 | 01/23 | Genome overview | 01/25 | Genome browser I<br>● PS1 Assigned |
| 2 | 01/30 | Histone code<br>● JC1 | 02/01 | Genome browser II |
| | | | 02/02 | - OPTIONAL FRI SECTION - |
| 3 | 02/06 | Polycomb & Trithorax<br>● PS1 Due | 02/08 | Genetic basis of disease<br>● Capstone Project Assigned |
| 4 | 02/13 | 3D Nucleus | 02/15 | CRISPR therapeutics I<br>● PS2 Assigned |
| 5 | 02/20 | Insulators & enhancers<br>● JC2 | 02/22 | CRISPR therapeutics II |
| | | | 02/23 | - OPTIONAL FRI SECTION - |
| 6 | 02/27 | Transcription | 02/29 | ASO therapeutics I<br>● PS2 Due, PS3 Assigned |
| 7 | 03/05 | RNA splicing<br>● JC3 | 03/07 | ASO therapeutics II |
| | 03/12 | NO CLASS | 03/14 | NO CLASS |
| 8 | 03/19 | RNA localization | 03/21 | Scientific illustration<br>● PS3 Due |
| | 03/20 | - OPTIONAL WED SECTION - | | |
| 9 | 03/26 | Epigenetic inheritance | 03/28 | Concept Proposals Review<br>● Concept Proposals Due |
| 10 | 04/02 | Non-coding RNA<br>● Revised Proposal Due | 04/04 | CRISPR therapeutics, *from the expert* |
| | | | 04/05 | - OPTIONAL FRI SECTION - |
| 11 | 04/09 | Translation | 04/11 | ASO therapeutics, *from the expert*<br>● Capstone Poster Due |
| 12 | 04/16 | ● Capstone Poster Session I | 04/18 | ● Capstone Poster Session II |
| 13 | 04/23 | ● Capstone Poster Session III | | |

● Journal Club (JC) Assignment ● Problem Set (PS) Assignment ● Capstone Assignment

## Assignments

*Journal Club*

*Updated 02/06/2024: The pre-class JC assignment was revised to better support students in meeting the course objectives. Please read.

### Why?

Reading primary research publications is ***hard***. But learning how to read primary research publications is ***important***.

You will need to read primary research publications for your capstone project and we want to help you develop this critical skill.

### Pre-class comprehension questions

*Due day before class (Monday at midnight) via Canvas*

Prior to class, spend time reading and preparing for the in-class journal club discussion, as follows. **1)** Read the publication thoroughly, making sure to spend time analyzing and considering ***the data in the figures*** in addition to reading the author's text, and **2)** complete the pre-class comprehension questions in Canvas to test your understanding.

Paper Reading #1 (● JC1 Due 01/29)

> Litt MD, Simpson M, Gaszner M, Allis CD, Felsenfeld G. Correlation between histone lysine methylation and developmental changes at the chicken beta-globin locus. Science. 2001 Sep 28;293(5539):2453-5. doi: 10.1126/science.1064413. PMID: 11498546. [Link]

Paper Reading #2 (● JC2 Due 02/19)

> Farley EK, Olson KM, Zhang W, Brandt AJ, Rokhsar DS, Levine MS. Suboptimization of developmental enhancers. Science. 2015 Oct 16;350(6258):325-8. doi: 10.1126/science.aac6948 PMID: 26472909. [Link]

Paper Reading #3 (● JC3 Due 03/04)

> Felber BK, Orkin SH, Hamer DH. Abnormal RNA splicing causes one form of alpha thalassemia. Cell. 1982 Jul;29(3):895-902. doi: 10.1016/0092-8674(82)90451-2. PMID: 7151175. [Link]

### Our advice

**Grading**

| | |
|---|---|
| **Journal Club** | **15%** |
| ● JC1 - Histone Code | 5% |
| ● JC2 - Insulators, enhancers | 5% |
| ● JC3 - RNA Splicing | 5% |
| **Problem Sets** | **30%** |
| ● PS1 - Genome Browser | 10% |
| ● PS2 - CRISPR Module | 10% |
| ● PS3 - ASO Module | 10% |
| **Capstone Project** | **25%** |
| ● Concept proposals | 5% |
| ● Revised proposal | 2.5% |
| ● Poster design and content | 10% |
| ● Poster presentation | 5% |
| ● Peer evaluation | 2.5% |
| **Breakout Sessions** | **30%** |

Expect it to be challenging. Read the journal club papers early and slowly. Step away and come back if you lose focus. Read them more than once. Look up words and methods you are unfamiliar with.

Reading the text will help you identify what was known and unknown at the start of the study ('Introduction'), how the techniques work ('Methods'), the author's description of the experimental data ('Results'), and the author's interpretation of the data ('Discussion').

But don't *just* read the text! ***Spend a significant amount of time evaluating the data figures for yourself.*** What do *you* think the data shows? How do *you* interpret the data? Do you agree or disagree with the author's conclusions and why?

Even after all this effort, there will likely still be things you are unsure about. That's okay. It's that way for us too. We will learn from each other in class.

### Resources for extra help

- Carey MA, Steiner KL, Petri WA Jr. Ten simple rules for reading a scientific paper. *PLoS Comput Biol.* 2020 [Link]
- Visit the teaching team at drop-in hours
- It is okay to discuss the paper with peers prior to class, but you must submit your own answers to the pre-class questions.

## *Problem Sets*

*Updated 02/06/2024: The due dates of PS2 and PS3 have been extended to allow additional time for completion. Please note the updated due dates below.

### Why?

Problem sets are designed to i) ***apply***, ***solidify***, and ***enrich*** lecture concepts, ii) test your understanding of the material and further develop your critical thinking skills, and iii) help identify areas that need additional clarification prior to the capstone project.

These assignments are to be completed independently; collaboration with peers is now allowed. Remember - there are no exams in this course (yea!) so treat the problem sets as take-home exams. You have free access to lecture notes and written resources and ample time. If the problem set exposes a gap in your understanding of the material, visit drop-in hours to have the lecture material clarified. But note that answers to problem sets will not be given during drop-in hours or discussion sections.

- Problem set #1: Genome browser (● PS1 Assigned 01/25, Due 02/06)
- Problem set #2: CRISPR Module (● PS2 Assigned 02/15, Due 02/29*)
- Problem set #3: ASO Module (● PS3 Assigned 02/29, Due 03/21*)

### Our Advice

Start early. Problem sets will be made available at the beginning of the module. It can be helpful to read through the problem set even before the material is covered in class.

You may not work on problem sets with peers, but you can access written resources as needed.

Bring your questions to drop-in hours. We will not give answers to problem sets, but will try to clarify any misunderstandings or provide additional resources to help, if needed.

*Capstone Project*

As a capstone project, you will draw upon insights acquired from bench and bedside sessions to design a practical therapeutic strategy for a genetic condition of your choice, which will then be presented to the class in the form of a scientific poster session.

1) You will use primary research publications and the genome browser to build a hypothesis for how a disease-causing mutation may impact the expression of the affected gene.
2) You will identify and design a CRISPR or ASO-based gene therapy method that could be used to correct the disease.
3) You will use BioRender to clearly convey the background and approach for your therapy in a visually appealing poster format.
4) You will present your poster at an in-class scientific poster session to your peers and teaching staff, and engage with the posters of your peers.

### Why?

***Curiosity*** and ***creativity*** are foundational for scientific discovery. Follow your curiosity as you deeply explore a genetic disease of your choosing. Creatively apply current approaches to therapeutically modulate gene expression.

Additionally, this provides an opportunity to i) practice scientific communication and scientific illustration and ii) ***synthesize*** information learned across the semester and ***showcase*** your accomplishments!

### Project components

- Concept proposals (🔴 Due 03/28)

  Choose two genetic diseases that could potentially be treated by a CRISPR or ASO therapeutic approach (you can be creative). For each, write an abbreviated abstract of the approach and make a graphical summary.

  *Abbreviated abstract*

  Write a two-paragraph abstract. In the first paragraph, describe the genetic basis of the disease and how it may affect gene expression or function. In the second paragraph, write a short rationale for the type of therapeutic design that may be used to treat the disease and the principle of your design.

*Graphical summary*

Make a graphical overview of your approach to accompany the abbreviated abstract. Learning how to represent scientific concepts in a visual form is an important skill in science communication. To aid in the representation of your capstone project idea, you will be introduced to BioRender, a free science illustration software. You will then practice the principles of graphic design in BioRender by creating a graphical overview of the genetic disease and the principle of your therapeutic design

In class, you will share your two abstracts in small groups and further hone your ideas with peer feedback. At the end of the class period, you will select one abstract to further develop into your capstone project.

- Revised concept proposal (🔴 Due 04/02)

  Select your best abstract to further develop into your capstone project. Further refine and revise your approach based on any comments / feedback.

- Capstone poster (🔴 Due 04/11)

  Use BioRender to build graphical representations of the background and approach for your project. Incorporate genome browser analysis of your gene of interest into your presentation. Use support from primary research publications to support your therapeutic design.

  For equity purposes, everyone will turn in an electronic copy of their final poster on this date, which will be used for grading the poster design and content.

- Poster session (🔴 04/16 - 04/23)

  The date of your presentation will be determined by random selection in class on 04/11.

  On the day of your presentation, you will hang up your poster and present it to peers and teaching staff as they circulate the room similar to the style of poster sessions at scientific conferences. At the poster sessions for which you are not presenting, you will engage and evaluate the posters of your peers. Full participation is expected at all poster sessions.

## *Breakout Sessions*

*Updated 02/06/2024: This section on breakout sessions was revised to better support students in meeting the course objectives. Please read.

**Why?**

The lectures in this course are not meant to be passive learning experiences; rather, the instructors will regularly pose questions for discussion. There will be multiple opportunities to

participate in each lecture, either in small group or large group formats. In-class 'breakout session' activities are meant to encourage students to i) be engaged in class and ii) practice applying concepts in a low stakes format so both students and teachers can identify gaps in knowledge and insufficiencies that should be addressed prior to graded assessments like the problem sets and capstone project.

**Breakout session activities**

Regularly, we will have small group 'breakout sessions' in which students will apply course material in a practical way. The format of individual activities will vary to meet the intended objective, but will frequently involve answering basic questions to worksheets provided in class. The breakout session will be limited to a designated amount of class time. Any unfinished work should be completed after class; completed activities *are due prior to the next class (3 PM) via Canvas* at which point the answer key will be released for students to check their own work.

If you will miss class due to sickness or other excused absence, email the teaching staff prior to your absence and you will be provided the link to the breakout session activity. Any student (whether in class or not) who submits the completed worksheet by the due date will be given credit. We are unable to accommodate individual extension requests, and will therefore automatically "excuse" two missing or incomplete worksheets, no questions asked, at the end of the semester.

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**Sections (Optional)**

There are four optional sections led by the teaching fellows if you would like additional opportunities to interact with course material, reinforce and extend concepts presented in class, and ask questions. Sections will not focus on the problem set questions specifically; no answer to problem sets will be presented.

Friday 02/02, 3 - 4 PM, Harvard Hall 201, led by Serafina Nieves
Friday 02/23, 3 - 4 PM, Harvard Hall 201, led by Aditi Limaye
Wednesday 03/20, 5-6:30 PM, Harvard Hall **202**, led by Rishabh Kapoor
Friday 04/05, 3 - 4 PM, Learning Lab (50 Church Street Suite 308), Capstone help session, including graphics support by Alexa Perez-Torres

**References**

There is no assigned textbook for this course. All supplemental reading materials and resources, including primary research publications, will be provided.

The following book is recommended as a resource but is not required. An electronic copy of this book is available in the Harvard Library Reserves (listed under course Canvas site).

Lewin's Essential Genes, 4th edition, 2021. Authors: Jocelyn E. Krebs, Elliott S. Goldstein, Stephen T. Kilpatrick

**Course Logistics**

*Academic Integrity and Honor Policy*

While this course promotes collaboration between students, it follows the Harvard Honor Code that expects students to solely submit their own work, as follows. *"Members of the Harvard College community commit themselves to producing academic work of integrity – that is, work that adheres to the scholarly and intellectual standards of accurate attribution of sources, appropriate collection and use of data, and transparent acknowledgement of the contribution of others to their ideas, discoveries, interpretations, and conclusions. Cheating on exams or problem sets, plagiarizing or misrepresenting the ideas or language of someone else as one's own, falsifying data, or any other instance of academic dishonesty violates the standards of our community, as well as the standards of the wider world of learning and affairs."*

*Policy on the use of artificial intelligence (AI) tools*

We specifically forbid the use of ChatGPT or any other generative artificial intelligence (AI) tools on assignments and projects in this course. Violations of this policy will be considered academic misconduct. We draw your attention to the fact that different classes at Harvard could implement different AI policies, and it is the student's responsibility to conform to expectations for each course.

*Attendance Policy*

Attendance at class is required and incorporated into breakout session grading, which is completed in class. If you are sick, email the instructors as soon as possible (at least 30 minutes prior to class) and they will arrange an alternative assignment. Failure to make arrangements in advance of class will result in no credit for the missed breakout session.

*Late Work Policy*

Late work will be deducted 10% of the total score per day late until the answers are made available, at which point no credit will be given. [Note, the answers to breakout session activities will be made available on the due date, so late submissions will not be accepted.]

*Accommodations for Students with Disabilities*

Harvard University values inclusive excellence and providing equal educational opportunities for all students. Our goal is to remove barriers for disabled students related to inaccessible elements of instruction or design in this course. If reasonable accommodations are necessary to provide access, please contact the Disability Access Office (DAO).