The Chemistry, Biology, and Societal Implications of Genome Editing

Chem 177
Harvard University, Fall 2024
Fridays 3-5:45pm, Pfizer Lecture Hall (Mallinckrodt 023), 12 Oxford St, Cambridge

Overview

The life sciences and medicine are undergoing a revolution stimulated by breakthrough advances in genome editing technologies. These technologies, including those enabled by CRISPR systems, enable researchers and physicians to modify target DNA sequences in the genomes of living cells, including those in plants, animals, and human patients. This class will overview the chemistry and biology underlying recent and current genome editing agents. We will also discuss their current limitations, how they are reshaping medicine and agriculture, and some social and ethical implications of their use. In addition to attending lectures that present the chemistry and biology of genome editing, students will analyze recent reports from the scientific literature, and will present their analyses and reasoned opinions during the semester. Participants will also develop and present final projects on an aspect of genome editing to the class at the end of the semester. For advanced undergraduates and graduate students with undergraduate-level understanding of molecular biology and either organic chemistry or biochemistry.

Instructors

David Liu is the Richard Merkin Professor and Core Faculty Member at the Broad Institute, Thomas Dudley Cabot Professor of the Natural Sciences and Professor of Chemistry and Chemical Biology at Harvard, and a Howard Hughes Medical Institute Investigator. He graduated from Harvard College in 1994 and earned his Ph.D. at U. C. Berkeley in 1999 before starting as an Assistant Professor at Harvard the same year. He has previously taught genome editing (Chem 177), chemical biology (Chem 170), Molecules of Life (SLS 11), organic chemistry (Chem 27), an integrated introduction to the life sciences (Life Sciences 1a), and a freshman seminar on gene editing (50Z). He has been awarded three university-wide teaching distinctions at Harvard: the Roslyn Abramson Award in 2003, the Joseph R. Levenson Memorial Teaching Prize in 2007, and a Harvard College Professorship in 2007. David's research group integrates chemistry and evolution to illuminate biology and enable new therapeutics, including the development of widely used genome editing technologies such as base editing and prime editing.

David R. Liu (drliu@fas.harvard.edu)
Office: 75 Ames Street, Room 3013

Ana Cristian (teaching fellow) is a fourth-year Ph.D. student in the Harvard-MIT Health Sciences and Technology program conducting research in the Liu laboratory. She graduated from the Georgia Institute of Technology in 2021 with a B.S. in Biomedical Engineering, during which she served as a teaching assistant for BMED 3110: Quantitative Engineering Physiology Laboratory I and tutored for multiple courses including differential equations and biotransport. Ana conducted undergraduate research with Prof. James Dahlman using DNA barcoding for high-throughput screening of novel lipid nanoparticle formulations *in vivo*. As an NSF Graduate Research Fellow in the Liu lab, Ana is now working on developing genome editing therapeutics to treat neurodegenerative disorders.

Ana Cristian (acristia@broadinstitute.org)

Reese Caldwell (teaching fellow) is a second-year Ph.D. student in the Harvard Biological and Biomedical Sciences program conducting research in the Liu laboratory. He graduated from Harvard College in 2023 with an A.B. in Human Developmental and Regenerative Biology, during which he served as a course assistant in SCRB 10. Reese did undergraduate research with Prof. Ryan Flynn to investigate the emerging phenomena of cell-surface (glycosylated) RNA. Reese previously worked as a Business Development and R&D Strategy Analyst at Biohaven Pharmaceuticals, where he led scientific evaluations of several drug candidates now in clinical trials for autoimmune disease, pain, and cancer. As an NSF Graduate Research Fellow in the Liu lab, Reese is now working to understand and improve upon the mechanism of genome editing agents.

Reese Caldwell (rcaldwell@g.harvard.edu)

Prerequisites
Undergraduate molecular biology and either organic chemistry or biochemistry.

Lectures and Discussions
Each course meeting will involve a lecture about a specific topic related to genome editing followed by student-led literature presentations and discussions on selected scientific literature relevant to that topic. Papers and presenters for the whole semester will be assigned at the beginning of the course.

Office Hours
The TFs will hold office hours immediately after lecture in the Pfizer Lecture Hall. Additional office hours via Zoom or in person are available upon request for Professor Liu and the TFs.

Final Projects
Each student will propose, develop, and present a final project on a topic covered in the course. Projects can take the form of a research proposal, a mini review articles on a specific topic relevant to the course, a computational analysis, a well-reasoned policy essay, or many other possibilities. Projects that take unusually creative forms—for example, original music, stop-motion animation shorts, a smartphone app, or a screenplay—are also welcome, but also must include a written explanation of how the project reflects scientific content from the course. Students are encouraged to discuss final project proposal ideas with course instructors throughout the semester, and to meet with teaching fellows no later than Nov 22 to discuss an outline of their final project prior to formal presentation of their project during the Dec 6 and Dec 13 class meetings.

Grading
Course grades will be based on lecture and discussion participation (1/3), on student literature presentations of assigned papers (1/3), and on final projects (1/3).

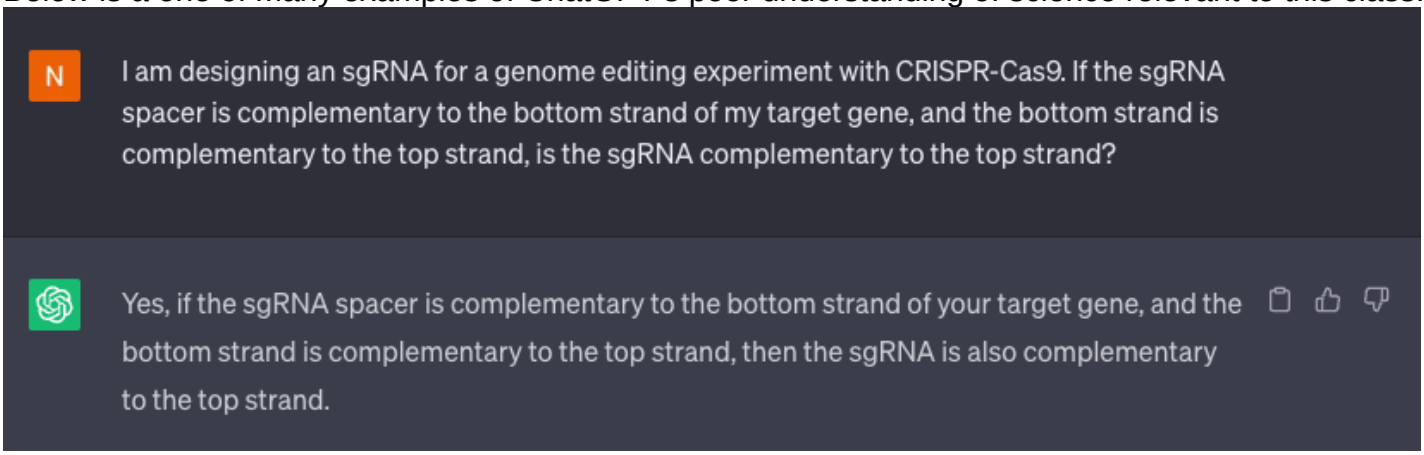
Academic Integrity Policy
You are expected to attend all course meetings in-person, participate in discussions, and refrain from distracting behavior in class or section. If you have professional conflicts (job interviews, etc.) or other extenuating circumstances, please discuss them with the instructor and we will develop a plan to resolve the conflict. Please review Harvard's Plagiarism Policy (available online), which describes the university's rules on coursework and collaboration.

Accommodations Policy
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). Accommodations do not alter fundamental requirements of the course and are not retroactive. Students should request accommodations as early as possible, since they may take time to implement. Students should notify DAO at any time during the semester if adjustments to their communicated accommodation plan are needed.

Generative AI Policy
Generative AI tools such as ChatGPT cannot yet reliably produce accurate information, especially about advanced science topics. These technologies can output 'hallucinated' information, illogical connections, and citations to papers that do not exist. You are responsible for verifying through reputable sources any idea not directly arising from course materials that guides your thinking. Importantly, *all work submitted in this course must be produced by you, not by an AI tool.*

Below is a one of many examples of ChatGPT's poor understanding of science relevant to this class.



Lecture Schedule (subject to change)

Meeting	Date	Topic	Presentations
1	9/6/24	Introduction and information flow in living systems	1 example paper
2	9/13/24	Zinc fingers, TALE arrays, ZFNs, and TALENs	3 papers
3	9/20/24	CRISPR nucleases: discovery and applications	3 papers
4	9/27/24	Base editing: development and applications	3 papers
5	10/4/24	Prime editing: development and applications	3 papers
6	10/11/24	Off-target genome editing and how to minimize it	3 papers
7	10/18/24	Transcriptome and epigenome editing	3 papers
8	10/25/24	Genome editing in agriculture	3 papers
9	11/1/24	Genome editing in therapeutics	3 papers
10	11/8/24	Genome editing in synthetic biology	3 papers
11	11/15/24	Genome editing commercialization, ethics, and other societal issues	3 papers
12	11/22/24	Student final project proposals (5 minutes each)	Project proposals
13	12/6/24	Presentation of student final projects (first half)	Final projects
14	12/13/24	Presentation of student final projects (second half)	Final projects