Advanced Undergraduate Seminars

Spring 2021

7.342 How Cells Perform Amazing Functions and Evolve to Overcome Challenging Environments
Instructor: Idan Frumkin (frumkini@mit.edu, 617-335-4294, laboratory of Michael Laub)
Spring 2021. Wednesdays, 10 am-12 pm. (Class day and time are flexible.) Possibly remote.

Cells must perform an enormous number of complex functions to survive ever-changing environments. To what degree can cells be considered to be optimized? Why do mechanisms of cell biology sometimes seem arbitrary and overly complicated? How could evolution have ever produced something as complex as a eukaryotic cell? Although the cell is commonly referred to as "the most basic unit of life," it is actually so complex that despite over 350 years of research we are still far from fully understanding its structural, functional and evolutionary workings. Bringing together the fields of cell biology and evolution into an integrated field of "evolutionary cell biology" provides a powerful perspective for studying mechanisms that produce cellular functions. This field offers insight into the evolutionary bases behind variations in cellular functions, significantly advancing our understanding of the fundamental principles governing cellular systems. An early example of evolutionary cell biology is the endosymbiotic theory of how mitochondria arose, a concept that revolutionized our understanding of the origins and structure of eukaryotic cells. In this course, we will discuss biological principles that have driven the adaptation of cellular functions, pathways, and structures. Questions we will explore include: How can cells optimize their gene expression patterns? How do core cellular machineries adapt to changing physiological and environmental needs? How do they expand their signaling capacity within already complex networks? How can phenotypic plasticity facilitate the evolution of novel cellular functions? How can comparative biology reveal novel functions for both well-studied and uncharacterized proteins? Are all observed cellular phenotypes functional, or can we detect the work of neutral evolution? How do new genes and new cellular functions emerge in evolution? Does cellular evolution help reduce the frequency of genetic diseases? By reading and critiquing the primary scientific literature, we will answer these questions and also learn how to (i) identify an important biological problem to study, (ii) rigorously design experiments, (iii) critically assess experimental data, and (iv) learn what challenges face biologists today. Students not only will gain insights concerning cutting-edge biological questions in cellular evolution but will also acquire essential soft skills for the modern biologist.

7.343 Food for Thought: How Metabolism Controls Cancer Cell Biology
Instructors: Alicia Darnell (adarnell@mit.edu, 5-4523; laboratory of Matthew Vander Heiden)
Evan Lien (elien@mit.edu, 5-4523; laboratory of Matthew Vander Heiden)
Spring 2021. Tuesdays, 12 pm - 2 pm. (Day and class time are flexible.) Possibly remote.

Metabolism is a process carried out by thousands of chemical reactions through which cells break down nutrients like sugars to generate energy and use this energy to synthesize complex molecules like proteins, lipids, and nucleic acids. Though the key pathways in metabolism were discovered more than 50 years ago, it is far from the passive reaction map sometimes depicted on wall charts – metabolism is fascinatingly unique in different cell types, and is rapidly adaptable to both external and internal stresses. Once viewed as the simple end product of enzyme expression and regulation, metabolite levels in fact can control many cellular processes, including gene expression itself. These new insights into the active role of metabolism in cell biology have also illuminated its fundamental contributions to the pathology of human disease. Cancer provides a striking example of a disease driven by alterations in metabolism – cancer cells depend on changes to nutrient utilization to support their survival, growth, and uncontrolled proliferation. In this course, we will examine how the role of metabolism in cancer and ask: Why do tumors consume more sugar than normal tissues? How do the genetic mutations that lead to cancer re-wire cellular metabolism? What determines the nutrients available to cancer cells, and how does this local nutrient environment shape their metabolic strategies for proliferation? How does metabolism control more complex disease phenotypes like metastasis and drug resistance? And finally, can we target the idiosyncratic and essential metabolic traits of cancer to improve disease therapy and outcomes? As we explore these topics, students will learn (1) how to digest, discuss, and critically evaluate the primary research literature, (2) both time-tested and cutting-edge experimental methods to tackle questions about metabolism in biology and medicine, and (3) how recent findings in cancer biology have challenged the traditional textbook understanding of metabolism. During each class, we will discuss two primary research papers with a focus on the logic, experimental methods,

and rigor of the interpretations. In addition to weekly active participation in these discussions, students will complete a written assignment mid-semester and an oral presentation at the end of the semester. We will discuss with a panel of experts how they have applied recent discoveries about metabolism to their careers in research, medicine, and drug discovery. We also will take a (likely) remote field trip to a local laboratory to learn more about the techniques and equipment used in cancer metabolism research.

7.345 Peptides and Nucleosides: Structures, Synthesis and Therapeutic Strategies

Instructors: Christine Arbour (arbour@mit.edu, 617-253-0206, laboratory of Barbara Imperiali)
Leah Seebald (lseebald@mit.edu, 617-253-0206, laboratory of Barbara Imperiali)
Spring 2021. Thursdays, 11 am – 1 pm. (Class day and time are flexible.) Possibly remote.

Peptides and nucleosides are ubiquitous building blocks in biology. These biomolecules have been an inspiration for modern pharmaceutical development, playing important roles as drug scaffolds and as tools for drug delivery modalities. In this course, we will discuss broad aspects of peptide and nucleoside chemistry and biology. We will emphasize how the structures of and synthetic approaches to these biomolecules influence the trajectory of therapeutic development and applications. The main challenge to assembling these biomolecules chemically is the available synthetic toolbox, which lacks sophisticated peptide and nucleoside methodology. This problem has led to developments of new "greener" synthetic strategies, i.e. aqueous based as opposed to using excessive amounts of chemicals that have poor atom efficiency for transformations. (Poor atom efficiency means that the chemical components of reagents are not incorporated into the final desired compound, resulting in excessive chemical waste.). These greener strategies will both facilitate scaling to an industrial pharmaceutical setting and have a positive environmental impact. Examples of peptides important to pharmaceutical development include cell-penetrating peptides, cyclic peptides used as immunosuppressants, and post-translationally modified peptides that alter peptide pharmacokinetics. Examples of post-translational modifications include glycosylated peptides, amino acids that contain functionalized sugars through *O*, *S*, and *N*-atom linkages, and disulfide-bonds (which involve the oxidization of and linkage between two cysteines residues within a peptide sequence or between two peptide fragments). Posttranslational modifications are integral in the production of an important peptide hormone, insulin, the major treatment for diabetes. Similarly, nucleosides are the precursors of natural products that possess a variety of biological activities -- including antibacterial, antiviral, and antitumor properties -- and serve as important scaffolds for drug development. We will discuss how nucleosides are incorporated as building blocks into natural nucleic acids, e.g., DNA and RNA. We will then compare the structures and syntheses of artificial nucleic acids. We will consider locked nucleic acids (LNAs) that have a ribose-bridging methylene between the 2' oxygen and 4' carbon, and peptide nucleic acids (PNAs) that have an amino acid-nucleoside hybrid structure substituting the phosphate backbone. These modifications can enhance the chemical stability and delivery of nucleic acids, which makes these biomolecules important scaffolds for current and developing therapeutics, such as anticancer agents and in vaccine development. Nucleic acid-based vaccines are a new generation of vaccines that carry the instructions to express a viral antigen protein that can train the body to elicit an immune response. Currently nucleic acid-based vaccines, such as mRNA vaccines, are the front runners for reducing the spread of SARS-CoV-2 in the current pandemic. Nucleic-acid vaccines are faster to develop because they circumvent the need to produce pure viral proteins on an industrial scale, reducing the time it takes to scale for mass production. By studying how peptides and nucleosides serve as the foundations for many emerging biotechnologies, students will gain a broad understanding of the interrelated fields of chemical biology and organic synthesis as well as a deeper understanding of the pivotal technologies upon which many local biotechnology companies are founded. This class will be entirely discussion-based and will focus on select articles from the primary research literature to facilitate conversations about the synthesis, structure, and applications of the molecules being considered. A major goal will be to learn how to critically analyze the primary research literature. This class will include both written and oral assignments based on relevant literature, and students will have the opportunity to visit (likely virtually) a local biotechnology start-up, where we will discuss current cutting-edge techniques and discoveries in peptide and/or nucleoside development.

7.346 Plants at War: How Conflicts Shape Plant Genetics, Molecular Biology, and Development

Instructors: Satyaki Rajavasireddy (satyaki@wi.mit.edu, 781-819-4075, laboratory of Mary Gehring)
Rebecca Povilus (rpovilus@wi.mit.edu, 248-953-1498, laboratory of Mary Gehring)
Spring 2021. Thursdays, 1 pm – 3 pm. (Class day and time are flexible.) Possibly remote.

Plants might appear to be passive fixtures in the environment. However, these often over-looked organisms are constantly engaged in battles against a wide variety of assailants on scales small and large – from genomic to ecological. This course will take a plant's-eye-view of three main types of conflicts, and in doing so will explore core concepts across genetics and molecular and developmental biology. First, we will examine how plants deal with other organisms in the race for resources. We will discuss how parasitic plants hijack resources and genes of their hosts, how the plant immune system uses RNA-silencing to confront viral pathogens, how mutually-beneficial partnerships with bacteria that live inside roots are negotiated, and how plants use molecular signals to manipulate their environments to defend precious resources. Second, we will focus on conflicts during reproduction. We will explore the race among male gametes as they search for egg cells, as well as the struggle between parental genomes as each tries to maximize its own fitness while fighting over how maternal resources are invested into seeds. We will start with classic interploidy-cross experiments that uncovered this interparental conflict by altering parental genome dosage in the offspring, then look at more recent discoveries about how gene dosage, genetic imprinting, and epigenetic modifications are involved, and finally explore how this tug-of-war between mothers and fathers can lead to the creation of new species. Third, we will examine conflicts that occur within an individual plant, both during development and within the genome. We will discuss the molecular signals plants use while deciding to allocate resources to vegetative (leaves, branches) or reproductive (flowers, fruits) growth, and the resulting consequences for plant architecture and reproductive fitness. On a genomic scale, we will learn how selfish, self-replicating genetic elements known as transposons try to take over a plant's genome, and how some genes use a process called "meiotic drive" to manipulate the machinery behind chromosome segregation during meiosis to break the rules of Mendelian inheritance. We will focus on the primary research literature so that students will learn principles of experimental design and how to critically read a scientific paper. Students will analyze and prepare a written report about a paper of their own choosing, and then present and critique another paper to the class during an oral presentation. The course will include a field trip (in-person or virtual) to the Weld Hill plant biology research facility at Boston's Arnold Arboretum. Overall, this course will use plant biology not only as a context for learning about emerging topics in biology but also as an introduction to the dynamic, surprising, and often beautiful nature of plants.