

Fall 2021

7.341 Evolutionary Cell Biology: How Cells Perform Amazing Functions and Evolve to Overcome Challenging Environments

Instructor: Idan Frumkin (frumkini@mit.edu, 617-335-4294, laboratory of Michael Laub)

Fall 2021. Tuesdays, 1-3 pm. (Class day and time are flexible.)

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 has generated insights 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 and severity 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 cell and evolutionary biologists today. Students not only will gain insights concerning cutting-edge biological questions in cellular evolution but will also acquire essential soft skills important for all modern biologists.

7.342 Immune Cell Migration: On the Move in Response to Pathogens and Cancer Immunotherapy

Instructor: Tim Fessenden (tfessend@mit.edu, 415-302-5009, laboratory of Stefani Spranger)

Fall 2021. Wednesdays, 9:00 am – 11:00 am. (Class day and time are flexible.)

The mammalian immune system is sometimes called a “liquid organ,” capable of rapidly initiating and then resolving potent responses to pathogens at almost any location in the organism. To accomplish this feat, the cells of the immune system must execute their functions in the right place at the right time, moving efficiently through a wide range of environments to ensure appropriate location and timing of their functions. What protein machinery drives immune cells’ rapid migration? How do cells make pathfinding decisions around barriers? How do they find rare pathogens or target cells in complex environments? This course will begin by examining the general immunological functions of two major immune cell types -- T cells and dendritic cells. We will then explore three aspects of T cell and dendritic cell function: (1) the biochemical sensors and mediators that compel immune cell motility, (2) the physical properties of cells and the structural proteins that drive their movements, and (3) the striking scale of immune system function, exemplified by structures that comprise many thousands of migrating cells during inflammation. Each of these aspects will be considered in the context of the adaptive immune response to tumors, which involves sequential recruitment of immune cells with specific functions and impacts on one another. Through our readings and discussions, we will examine the connections between immunotherapy as an emerging treatment modality for a variety of cancers and the migration of immune cells. Using the primary research literature as a base, students in this course will learn how to integrate rich mechanistic

detail established at subcellular and molecular scales with the large-scale powerful functions by which the immune system can respond to challenges anywhere in the body.

7.343 Single-molecule Imaging: Capturing Nanoscale Cellular Machines in Action

Instructor: Hazal B. Kose (koseh@mit.edu, laboratory of Steve Bell)

Fall 2021. Wednesdays, 3-5 pm. (Class day and time are flexible and will be decided based on students' schedules.)

Did you know that we have approximately 2 meter of DNA packed in our cells, which are less than 10 μm diameter? Or that to replicate DNA it is copied at a rate of 70,000 basepairs per second by a cellular apparatus that coordinates at least six different enzymes? Or that microtubules form greater than 1 meter long “railways” upon which molecular machines transport cargo within nerve cells? In this course, we will explore how single-molecule imaging techniques capture the mega-cellular machines working in real-time. Inside the cell, thousands of events are happening via dynamic interactions among single molecules, traveling through different compartments, and creating higher-order macromolecular behaviors. The organization and dynamics of these macromolecule structures --such as the replisome complex that mediates DNA replication; the RNA polymerase complex (RNAP) for transcription elongation; or the dynein complex that “walks” on microtubules and carries essential signals and organelles -- are often regulated through complex rules involving short-lived, weak, and highly dynamic interactions. Although biochemical assays have provided remarkable insight into the various activities of individual proteins and their collective action in these processes, monitoring the kinetics of individual steps is challenging, if not impossible using such assays. This limitation is primarily because biochemical assays of complex multicomponent events are intrinsically asynchronous, and these short-lived and dynamic interactions in complex multicomponent events are usually concealed when averaged over the ensemble. The development of single-molecule experiments has allowed scientists to study the detailed dynamics of individual biochemical events. Using precision nanotechnology techniques such as fluorescence microscopy, single-molecule FRET, magnetic tweezers, optical traps, super resolution microscopy -- all of which work at the level of single molecules -- scientists can now monitor the individual movements of proteins, and their one-on-one interactions with each other as they function. For example, we can see how fast and for how long each step of the process takes, monitor interactions of each protein (or even protein subunits!), reveal important differences between individual cellular machines, and determine how these machines deal with barriers on their path. Additionally, by combining approaches from physics, engineering, chemistry and biology, single-molecule tools possess an incredible power to discover the principles underlying intracellular order and mechanics, revealing new information about the fundamental physical and biochemical properties of living cells. During this course, students will learn: (1) how to read, discuss, and critically evaluate scientific findings in the primary research literature; (2) how cutting-edge single-molecule technologies are being used to reveal intrinsic details of fundamental cellular processes (primarily focusing on DNA replication, transcription, and cytoskeletal elements of cells); (3) advances and limitations of single-molecule techniques; and (4) how to identify, discuss, and propose experiments to address open questions in the field.

Spring 2021

7.341 Turning Evolutionary Dials: Biomolecular Design Strategies from Therapeutics to Climate Change

Instructors: Megan Kizer (mkizer@mit.edu, 617-299-0297, lab of Barbara Imperiali)

Robbie Wilson (rhwilson@mit.edu, 617-955-2465, lab of Matthew Shoulders)

Spring 2022. Tuesdays, 11 am -1 pm. (Class day and time are flexible.)

Over the course of millions of years, nature has been quietly at work to select highly efficient and specialized biomolecules that perform a vast myriad of tasks. Today, researchers can assume this historical role of nature. By precisely controlling aspects of the evolutionary process, we can develop similarly specialized and novel biomolecules that suit specific needs. Utilizing controllable systems and fine-tuning selection factors, biomolecules can be readily evolved to accelerate reactions, catalyze reactions with unconventional substrates, and bind new targets. Beginning with a population diversified with random mutations, evolution is achieved by

iteratively increasing selection stringency to obtain individuals with desired traits. Being able to drive and direct evolution has revolutionized the way in which we develop biomolecules. Now utilized in many biotechnological applications, and recognized by the 2018 Nobel Prize for Chemistry, directed evolution is truly a staple in biomolecular design. This course will cover the many ways in which we have realized evolution in the laboratory toward functional biomolecules, such as protein and nucleic acid-based therapeutics, enzymes that catalyze production of synthetic drugs, and carbon-dioxide capture molecules to lessen the impact of climate change. Students will both become familiar with the field of directed molecular evolution and learn how to critically analyze primary research papers, design research experiments and present data relating to molecular biology and evolution. The class will be entirely discussion based. Students will develop essential communication skills for careers in biological and biomedical sciences through a written assignment and an oral presentation. There will be a field trip to a local commercial or academic laboratory that utilizes directed evolution to generate exciting applied technologies. The importance of directed evolution in biomedical and biotechnological careers, both academic and industrial, will be highlighted. A breadth of opportunities to hone core scientific skills and explore the applied biological career space will be offered.

7.342 Let's Talk about Sex (Differences): The Evolution of Sex across Species and the Consequences of Sexual Differences for Human Health and Disease

Instructors: Abbie Groff (agroff@wi.mit.edu, 717-823-8102, laboratory of David Page)

Jordana Bloom (jbloom@wi.mit.edu, 201-921-3444, laboratory of David Page)

Spring 2022. Wednesdays, 1 pm – 3 pm. (Class day and time are flexible.)

In humans, individuals with two X chromosomes have a higher risk of developing autoimmune disease, whereas XY individuals tend to be more susceptible to infectious disease (highlighted most recently through the Covid-19 pandemic). What drives this difference? Culturally, we interact with the concept of sex (separate from gender) on a daily basis, but this familiarity, combined with historic scientific bias, has led to oversight in examining sex as a biological variable and the contribution of sex differences to development, aging, and disease. What do we mean by “sex”? Can sex be simplified into a core set of biological concepts? What influences the evolution and development of sex? What are sex differences? Why and how do they arise? How constant are the rules and mechanisms determining sex and sex differences across species, and how does our understanding of sex in humans influence the practice of medicine and the course of scientific discovery? This discussion-based course will explore the scientific literature to grapple with the evolutionary and cell biological perspectives on these questions as we examine both emerging and historic studies of sex differences. We will consider first what sex is as well as how it is determined and broadly represented across a variety of diverse organisms. Next, we will turn our attention to sex differences in human physiology and disease, interrogating the possible sources of variance (sex chromosomes, hormones, and environment) in turn. What types of experiments form the basis of our understanding of these phenomena? Students will learn to critically read and evaluate primary research articles, assess experimental design and alternatives for data visualization, and gain broad exposure to the myriad experimental techniques (such as Next Generation Sequencing, single-cell sequencing, and metabolomics) used to assess differences between the sexes. Assignments will include participation in class discussion, a written assessment, and a tiktok summarizing each student's independent research into a particularly interesting sexual dimorphism.

7.343 Why Humans Aren't Immortal: Molecular Mechanisms of Aging and Age-related Disorders

Instructor: Alexandra Pike (alexpik@mit.edu, 901-409-6170, laboratory of Steve Bell)

Spring 2022. Thursdays, 2-4 pm. (Class day and time are flexible.)

Humans and many other organisms experience the all too familiar process of aging, during which cells can lose their normal functions and regenerative capacity over time, causing age-related degeneration and disease. But how does this altered cellular function connect to recognizable features of aging, such as wrinkles, hair graying, and degenerative diseases? Why do some centenarians (people older than 100) have few health conditions, while some much younger adults succumb to age-related diseases? As we cure infectious diseases and other causes of mortality, how can we alleviate the symptoms of aging to increase one's healthspan? What differentiates a young

cell from an old cell in the human body? Can aged cells be reprogrammed to regain their youth? In this course, we will explore the biomedical science of aging. Researchers around the globe are studying both human populations and various experimentally tractable organisms to uncover the keys to aging. Many lines of investigation have converged on the central issues of identifying the genetic and environmental factors that lead to age-related degeneration and of identifying how these factors work at the cellular level. We will discuss a breadth of molecular mechanisms that have been implicated in the aging process over decades of research. For example, as cells divide many times, they lose the protective structures at the ends of chromosomes called telomeres. Telomere attrition causes cells to either undergo a programmed cell death called apoptosis or enter an irreversible cell cycle arrest called senescence. Senescent cells release inflammatory signals that can cause broad tissue damage. Many other molecular mechanisms lead to cellular senescence, including the accumulation of DNA damage, DNA replication stress, and altered protein homeostasis. Aging cells also undergo epigenetic changes – heritable phenotypic changes that do not involve DNA sequence changes – that alter gene expression profiles. Furthermore, there are a myriad of metabolic mechanisms of aging involving mitochondrial dysfunction and altered metabolic signaling. We will critique the experimental methods and logic that led to crucial discoveries surrounding our current understanding of the biology of aging. We will also discuss how laboratory findings have been translated into human populations and health, including various biotechnologies and other popularized lifestyle interventions purported to offset aging. This discussion-based course will focus on the primary research literature. Students will develop skills for reading and critically analyzing scientific journal articles, interpreting experimental data, and designing rigorous experiments and controls. Students will interact with researchers in the field of aging and visit a local biotechnology company or academic laboratory focused on the science of aging. The topics covered will introduce students to a variety of methodologies used not only in the aging field but across molecular medicine disciplines.