Advanced Undergraduate Seminars
2022-2023

Fall 2022

7.341 Microbes at War: The Mechanisms That Drive Infectious Diseases
Instructor: Lisa McLellan (lkmcl@mit.edu, 617–253–5393, laboratory of Alan Grossman)
Fall 2022. Tuesdays, 11 am-1 pm. (Class day and time are flexible.)

Your war against pathogenic microbes has begun. It started with a urinary tract infection that you countered by drinking lots of cranberry juice. The second attack was directed at your sense of smell and taste. Your body was in a fight with COVID19 which was won by your body's immunity T cells. You celebrate your victory over COVID19 with a hike and a steak dinner with friends. However, due to a tick bite you received on the hike, you had a severe allergic reaction to the beef! You have had a streak of extremely bad luck: Why did you lose your sense of smell? How can a tick bite cause a meat allergy? And did the cranberry juice to anything to help cure your urinary tract infection? To answer these and other questions, we are going to take a dive into the molecular world of microbes. In this class, we will use the primary research literature to explore the molecular interactions between pathogens and their hosts that allow microbes to cause infectious diseases. We will examine the factors that pathogens use to colonize a host and how the host response can impact the outcome of the infection. During this course, students will learn: (1) how various microbes interact with their hosts to cause diseases, (2) how the host responds in an attempt to stay healthy (and how this sometimes backfires!), (3) the methods researchers use to study these processes and, (4) how to critically read, evaluate, and discuss the primary research literature. We will highlight how microbes are important for and utilized in both academic, medical, and industrial biomedical careers. This will include a field trip to a commercial laboratory that develops exciting new microbial products to better human health. By the end of the class, students will have both developed critical scientific skills in evaluating scientific literature and an appreciation of the microbes influencing our lives and health every day.

7.342 Synapse Remodeling in Health and Disease
Instructors: Dalila Ordonez (ordonezd@mit.edu, 347-863-6816) & Josiah Boivin (jboivin@mit.edu, 765-506-3995) (laboratory of Elly Nedivi)
Fall 2022. Wednesdays, 1 pm - 3 pm. (Class day and time are flexible.)

Our brains are remarkably adaptable throughout our lives. Individual brain cells called neurons form synapses, sites of physical connection and communication between neurons, and then repeatedly rewire those connections in response to new experiences or to neuronal cell death caused by injury, disease, or aging. In this course, we will explore how neurons establish their synapses in the healthy brain during childhood and later in life, and how this process goes awry in disease states. More specifically, we will discuss how the brain forms its synapses early in life, stabilizes a subset of those synapses for long-term maintenance, and continues to add and remove synapses throughout life. We will then explore synapse dysfunction in diseases such as autism and Alzheimer's disease, which involve abnormal increases or losses of synaptic connections, respectively. We will also consider synapse remodeling, a process of adding and removing synaptic connections to optimize our brain network, in the context of neuroinflammation, recovery from traumatic brain injury, and psychological trauma following prolonged stress. This course will be discussion-based. Each session will provide an opportunity for students to tackle two related papers from the primary scientific literature, ask questions to hone their understanding of the methodology and data presented in the papers, and practice critiquing the papers. Students will also have an opportunity to build their written and verbal communication skills through a written assignment and an oral presentation. The written assignment will focus on proposing an experiment in a mock mini-grant proposal, which students will draft and then refine together during one of the class sessions. In the oral presentation, students will practice explaining and critiquing a paper from the scientific literature. To provide real-life experience with the techniques used in the papers we discuss in class, we will see a demonstration of brain imaging in an MIT neuroscience laboratory, which will exemplify the experimental methods needed to generate the scientific figures analyzed in class. To facilitate discussion about career paths in the biomedical sciences, we will go on a field trip to Vertex

Pharmaceuticals, where we will hear from industry scientists about their career journeys and learn about ongoing research behind neuromuscular diseases, including a family of rare genetic disorders characterized by muscle degeneration caused by alterations in the peripheral nervous system. This course will introduce students to a variety of methodologies used not only in the field of synapse dynamics but more generally across many disciplines in the field of molecular medicine. This class may be particularly beneficial to students interested in careers in biomedical research and/or medicine, but we welcome all students who are excited about learning how to read the primary scientific literature, understanding the process of critical scientific reasoning, and learning about how our brains remodel their connections in healthy and diseased states.

Spring 2023

7.341 The RNA World: From the Origin of Life to Modern Medicine
Instructor: Robert Battaglia (rabatt@mit.edu, 585-322-4760, laboratory of Gene-Wei Li)
Spring 2023. Wednesdays, 3 pm – 5 pm. (Class day and time are flexible.)

According to the RNA World hypothesis, all the complexity and diversity of life originated from simple polymers of a nucleic acid called RNA. Why RNA? RNA has the unique capacity to carry information from one generation to the next *and* perform catalysis. Scientists did not need a time machine to figure this out—several "living fossils" of the RNA World can be found playing key roles in central molecular processes across life today. Catalytic RNAs called ribozymes (a portmanteau of ribonucleic acid and enzyme) come in many flavors and are at the heart of machinery responsible for translation of RNA into protein and for splicing introns out of precursor mRNAs. Even when RNA is not performing catalysis, you can still find it directly involved in maintaining chromosome integrity, fighting viral invaders in bacteria (e.g., CRISPR), and tuning gene expression. Today you can find RNA at work in the doctor's office, too. From mRNA vaccines combatting COVID-19 to small RNAs silencing mutated genes in genetic diseases, RNA medicine is paving the way to new breakthroughs in the prevention and treatment of disease. In this course, we will read and discuss the primary research literature to follow the journey of RNA from its humble beginnings in the primordial soup to its involvement in fundamental biological processes and its emerging presence in the medicine cabinet. First, we will examine evidence for the RNA World hypothesis in the chemical and structural features of RNA. Then, we will see how these features facilitate the role of RNA in the biological processes described above. Finally, we will use the COVID-19 mRNA vaccines and the novel spinal muscular atrophy drug Spinraza as case studies for how RNA can be used as medicine. Along the way, students will learn how to design and critically evaluate experiments in RNA biology and give a presentation on an RNA-related topic of their choosing. The course will also include a field trip to a local biotechnology company working on RNA medicine.

7.342 **Dynamics of the Immunological Synapse in Health, Cancer, and Autoimmune Disease**
Instructor: Keith Eidell (eidellk1@mit.edu, 617-960-6547, laboratory of Mike Hemann)
Spring 2023. Thursdays, 2 pm - 4 pm. (Class day and time are flexible.)

The "immunological synapse" (IS) is an interface between immune-system cells such as T cells and Natural Killer cells and their corresponding target cells, e.g. pathogen-infected host cells and cancer cells. Recent work has demonstrated that the IS plays significant roles in the delivery of cytotoxic molecules, cytokines (molecules that can drive cell activation and cell proliferation) and inflammatory mediators. In this course we will discuss the nature of the IS, e.g. the subcellular structures present in both the immune cell and its corresponding target cell, and how biologists can engineer the IS to ramp up an immune response to combat cancer or, conversely, to turn down an immune response to combat autoimmune disorders. Chimeric Antigen Receptor (CAR) T cells provide a striking example of such therapeutic cellular engineering. First, a cancer patients' T cells are isolated from whole blood. These T cells are then engineered to specifically recognize and kill cells that express a specific, targeted cancer cell surface antigen. More specifically, a CAR is a chimeric receptor protein with the binding region of an antibody that recognizes a particular cancer antigen linked to the cytoplasmic signaling domain of a T cell receptor that drives T cell activation and killing of the targeted cell. For example, a CAR that targets malignant B

cells might consist of an extracellular domain derived from an antibody that recognizes a molecule (e.g. CD19) expressed specifically on the surface of cancerous B cells and an intracellular signaling domain that activates the T cell to kill the malignant B cell with which it interacts. Once constructed, the CAR is introduced into the patients' T cells, generating the CAR-T cells that are then infused into the patient, circulating throughout the patient's body and identifying and killing cancer cells. Such engineered CAR-T cells can be thought of as "living drugs" that have the ability to recognize and kill malignant cancer cells. CAR-T cells have proven to be highly effective at fighting different forms of B-cell-derived hematological cancers, such as leukemia. Additionally, cytotoxic CAR-T cells offer a novel approach for controlling autoimmune damage to heart tissue post-cardiac arrest. Following a heart attack, cardiac tissue will attempt to heal itself via the fibrosis of damaged heart tissue. However, excessive fibrosis can occur within the damaged tissue and result in severe and long-term damage. Recently, it has been demonstrated that cytotoxic T cells engineered to express a CAR receptor targeting a uniquely expressed surface protein on cardiac fibroblasts (Fibroblast Activation Protein, FAP) can reduce the level of fibrosis after a cardiac event. This work suggests that elimination of FAP-expressing cardiac fibroblasts by CAR-T cells might prevent long-term tissue damage. We will begin this course by discussing the first papers that described the structure of the immune synapse. We will then consider more recent discoveries concerning immune synapse function and how cellular engineering techniques can be combined with CAR technology to develop CAR-T therapeutics. Some current approaches to immune-system cellular engineering involve modifications to the CAR receptor within the cytoplasmic tail, providing new signaling motifs to enhance and broaden IS function. These new bioengineering approaches will hopefully not only lead to more effective cellular immunotherapy treatments targeting different forms of cancer but also might also prove effective for the treatment of autoimmune disorders.