Advanced Undergraduate Seminars
2022-2023

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 Moderna's Norwood, MA site.

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.