Advanced Undergraduate Seminars
2018-2019

Fall 2018

7.341 Biomaterials and Devices for Disease Diagnosis and Therapy

Instructors: Kevin McHugh (kjmchugh@mit.edu, 617-324-4868, laboratory of Robert Langer)
Ali Beyzavi (beyzavi@mit.edu, 617-963-9437, laboratory of Robert Langer)
Fall 2018. Tuesdays, 1 – 3 pm. (Class day and time are flexible.) Room 68-150.

The use of materials to solve healthcare challenges dates back to ancient times when simple prosthetics made of wood were used to augment the function of lost limbs. Over the past millennia our technological capabilities have advanced dramatically to the point at which we can now engineer complex biomaterial devices that integrate with cells, proteins, and other biological molecules to assess disease or elicit a desired therapeutic effect. This course will focus on biomaterials principles, such as biocompatibility, cell-protein interactions, controlled release, polymer modification, and self-assembly, with a particular emphasis on technologies that manipulate biologics at the micro- and nanoscale. Students will learn about the use of biomaterials to create advanced diagnostic tools for detection of infectious and chronic diseases, restore insulin production to supplement lost pancreatic function in diabetes, provide cells with appropriate physical, mechanical, and biochemical cues to direct tissue regeneration, and enhance the efficacy of cancer immunotherapy. By examining the primary literature, we will seek answers to key questions currently facing the field of biomedicine, including: What strategies can we use to make vaccines more potent? How can we use the immune system to specifically target cancer cells? How can we quickly (and inexpensively) diagnose disease? Is it possible to make a truly bioinert device? What tools are available to direct tissue regrowth and repair? Can we make nucleic acid delivery sufficiently to silence or correct genetic mutations? Through reading and in-class group discussion, students will develop the skills necessary to critically analyze papers. Students will also be tasked with using their creativity to ask new questions that build upon the concepts presented in the literature. By the end of the course, students should be able to evaluate the validity of methods used, identify key experimental controls, interpret figures, and draw their own conclusions about the importance of a manuscript. This course will also include a field trip to a local biotechnology company to expose students to state-of-the-art biomaterial strategies being employed in cell-based therapy. The goals of this course are for students to get a broad understanding of the field of biomaterials, develop the ability to independently evaluate scholarly manuscripts, and understand how to rationally design experiments of their own.

7.342 A Double-Edged Sword: Cellular Immunity in Health and Disease

Instructor: Haiting Ma (hma@wi.mit.edu, 615-525-4066, laboratory of Rudolf Jaenisch)
Fall 2018. Wednesdays, 11 am - 1 pm. (Class day and time are flexible.) Room 68-150.

Immune cells are a diverse group of cells that function as foot soldiers to protect our bodies from both self-derived threats and exogenous pathogens, while keeping peace with normal cells and non-harmful or beneficial commensal microbiota. Immune cells are equipped with a variety of powerful and adaptable mechanisms to detect and subsequently resolve a wide spectrum of insults, a capacity that is essential for maintaining homeostasis under normal physiological conditions. However, the same mechanisms can backfire upon immune evasion of invading pathogens or under physiological stress and instead propel progression into any of a series of severe disorders, such as immunodeficiency, chronic infection and inflammation, autoimmune diseases, allergy, degenerative diseases, and cancer. Basic and translational research studies of immune cells have led to novel strategies to treat some of these disorders. In this course, we will discuss the connections between normal physiology (defense against infections, immune surveillance, and homeostasis) and disease (immune deficiency, chronic inflammation, and autoimmunity) by examining primary research papers that range from the classic to the most recent. We will discuss the developmental relationship between innate and adaptive immune cells as well as the functions and malfunctions of both types of immune cells. Our topics will include both basic biological principles (such as inflammatory and non-inflammatory cell death and immune cell signaling) and clinical applications (such as immune checkpoint blockade and chimeric antigen receptor-T or CAR-T cells). This course will familiarize students with basic immunological regulatory mechanisms and examples of strategies that apply knowledge of

this fundamental biology to improve human health. More generally, students will learn how to identify relevant primary research literature, critically evaluate experiment data, and reach their own conclusions based on primary data. We also hope to have the opportunity to learn how fundamental knowledge can be translated into a therapeutic treatment by visiting a local pharmaceutical or biotechnology company that develops therapeutics based on immune cell biology.

7.343 Host-Pathogen Interactions: Biology and Disease Consequences of Parasite Hijacking

Instructors: Clare Harding (harding@wi.mit.edu, 617-324-5869, laboratory of Sebastian Lourido)
Diego Huet (dhuet@wi.mit.edu, 617-324-5869, laboratory of Sebastian Lourido)

Fall 2018. Wednesdays, 1 pm - 3 pm. (Class day and time are flexible.) Room 68-150.

Parasites must manipulate and subvert their hosts to survive. Such a pathogen scavenges nutrients directly from its host, evades the host immune system and can even modify host behavior to increase its chances of transmission. This course will explore the strategies used by a ubiquitous and harmful family of eukaryotic parasites called the Apicomplexa to hijack the biology of their hosts. The Apicomplexa include important human pathogens such as *Plasmodium* and *Toxoplasma,* responsible for some of the deadliest and most prevalent diseases on the planet as well as for a number of veterinary disorders. *Plasmodium* infection causes malaria and, despite huge efforts over the past 40 years, still leads to more than half a million deaths per year, mostly of children under five. As a pathogen of humans for the past 100,000 years, *Plasmodium* has evolved elegant strategies to survive and ensure its transmission, even altering the behavior of mosquitos to make them feed more often, increasing the transmission of the parasite. We will also study *Toxoplasma gondii*, which is arguably the world's most successful pathogen, infecting up to half the human population. Although its sexual cycle requires passage through cats, *Toxoplasma* is able to survive and replicate within almost all warm-blooded animals. In humans, *Toxoplasma gondii* causes a chronic and asymptomatic infection in most immuno-competent subjects. However, in immuno-compromised patients *Toxoplasma* infection causes blindness or fatal brain inflammation, while infection of otherwise healthy pregnant women can cause miscarriage and fetal abnormalities. Intriguingly, chronic *Toxoplasma* infection has been linked to behavioral alterations of its hosts. Infected mice lose their fear of cats, increasing their chance of being eaten and so completing the parasite's lifecycle. In humans, *Toxoplasma* infection has been linked to risk-taking behavior. By exploring how such pathogens invade a host cell and replicate while evading the immune system, students will gain a broad understanding of cell biology, biochemistry and cellular immunology as well as of state-of-the-art techniques used in molecular biology. We will critically analyze the primary research literature and have the opportunity to participate in a local parasitology symposium, where we will learn about the latest cutting-edge techniques and discoveries in the field of molecular parasitology.

7.344 Cellular Metabolism and Cancer: Nature or Nurture?

Instructors: Allison Lau (anlau@mit.edu, 5-4523; laboratory of Matthew Vander Heiden)
Evan Lien (elien@mit.edu, 5-4523; laboratory of Matthew Vander Heiden)

Fall 2018. Thursdays, 3 pm - 5 pm. (Day and class time are flexible; TBD at first class.) Room 68-150.

Cellular metabolism is frequently considered to be a thoroughly understood and largely static process by which cells metabolize nutrients to generate energy in the form of adenosine triphosphate (ATP). However, while the foundations of cellular metabolism have been clear for over 50 years, recent discoveries have shown that metabolism is a much more dynamic and malleable process than previously recognized. Although all cells have access to the same finite set of metabolic reactions, how these pathways are utilized is context dependent and is tailored to support the distinct functions of different cell types. One striking example is the metabolism of cancer cells, in which nutrient utilization must be re-wired to not only meet cellular energy demands but also to support cell proliferation, growth, survival, and metastatic capacity. In this course we will explore how altered metabolism drives cancer progression and ask: Why do tumors consume more sugar than normal cells? How is the proliferative metabolism of cancer cells different from the homeostatic metabolism of normal cells? How do alterations in cancer-associated genes re-wire cellular metabolism? Can environmental factors cooperate with genetic changes to drive the metabolic phenotypes of cancer cells? Are there metabolic interactions among cancer

cells, normal cells, and whole-body metabolism to contribute that the progression of the disease? How do metabolic processes support other malignant cancer characteristics, such as metastasis and drug resistance? As we explore these topics, students will learn (1) how to read, discuss, and critically evaluate scientific findings in the primary research literature, (2) how scientists experimentally approach fundamental issues in biology and medicine, (3) how recent findings have challenged the traditional "textbook" understanding of metabolism and given us new insight into cancer, and (4) how a local pharmaceutical company is developing therapeutics to target cancer metabolism in an effort to revolutionize cancer therapy.

Spring 2019

7.341 How DNA's Sister Does All the Work: The Central Roles of RNA in Gene Expression
Instructors: Ana Fiszbein (anafisz@mit.edu, 617-749-8096, laboratory of Chris Burge)
Marvin Jens (mjens@mit.edu, 617-383-0948, laboratory of Chris Burge)
Spring 2019. Wednesdays, 11 am -1 pm. (Class day and time flexible.) Room 68-150.

While most cells in the body have exactly the same DNA, cells differ drastically in how they use their DNA. RNA, which is transcribed from DNA, is front and center of this specificity of expression and regulation of genetic information. This course will explore the frontiers of the world of RNA biology using primary research papers to trace how the original odd detail sometimes led to major discoveries. We will discuss exciting discoveries about the unexpected diversity of RNA classes and the mechanisms by which they are generated and exert their function. For example, while DNA base-pairing is mainly used to replicate genetic information, RNAs employ base-pairing for a wider array of functions, including specific binding to other RNAs. We will first review and update our knowledge about the historically best characterized RNAs: messenger RNA (mRNA), transfer RNA and ribosomal RNA, which together employ base-pairing to read the genetic code and synthesize proteins. In many organisms mRNAs undergo a processing step called splicing, which allows for many alternative variant messages to be made from the same gene and explains how the human body can make over 100.000 proteins from only 20.000 genes. Splicing defects are involved in a broad variety of human disorders. We will then turn to more recently discovered small non-coding RNAs, such as microRNAs, siRNAs, and piRNAs, which regulate the functions of other genes and can change cell fates during development. Finally, we will discuss RNA species about which we still know very little, such as long non-coding RNAs and circular RNAs. Some long non-coding RNAs associate with chromatin, thereby altering the expression of other genes or bringing together different chromosomes in the nucleus. Circular RNAs are unexpected products of splicing that have no ends and are therefore very stable compared to other RNAs. Many circular RNAs might simply be by-products, but some exist in surprisingly large quantities and can alter regulation by microRNAs or RNA-binding proteins, in one case with very specific consequences on behavior. Also, some circular RNAs have the capacity to be translated and make small proteins, adding to the already vast protein diversity enabled by alternative splicing. As we discuss the exciting diversity of RNA functions and marvel at the wonders of RNA, we will critically analyze both landmark and very recent primary research papers. We will visit the biotechnology company Moderna Therapeutics, which develops artificial mRNAs that can be administered to patients as a drug to substitute missing mRNAs or activate genetic programs that are needed for recovery from injuries.

7.342 Cellular Organelles in Health and Disease
Instructors: Nora Kory (617-840-5206, nkory@wi.mit.edu, laboratory of David Sabatini)
Monther Abu-Remaileh (617-840-5206, monther@wi.mit.edu, laboratory of David Sabatini)
Spring 2019. Wednesdays 1 pm- 3 pm. (Day and class time are flexible.) Room 68-180.

The cell is the basic functional unit of life. Cells perform their diverse functions through a versatile series of biochemical reactions that require different chemical and physical environments. In eukaryotic cells, a complex compartmentalized system consisting of membrane-bound organelles allows these reactions to occur under optimal conditions and prevents accumulation of harmful metabolic intermediates in the wrong places. Additionally, these organelles are sites of signaling and metabolic regulation that enables cells to survive and perform their specialized functions in the body. In this course, we will explore the primary scientific literature to

learn about different organelles, including the nucleus, endoplasmic reticulum, mitochondrion, lysosome, peroxisome and the Golgi, in addition to the new emerging field of phase-separated compartments. We will study the biogenesis, biology, and specialized functions of organelles in different organs and tissues, like the function of mitochondria in powering muscle function in some types of muscle but not in others. We will also learn about human diseases that are caused by organelle dysfunction, e.g., storage diseases caused by mutations in lysosomal genes and congenital metabolic disorders in children with mitochondrial gene mutations. We will learn about the biochemical, molecular and cell biological techniques that scientists (including ourselves) use to study cellular organelles. While discussing these multiple aspects of organelle biology, we will learn about scientific reading skills and how to critically think about the scientific literature, identify open questions in the field, and articulate ideas in a research plan. We will visit a research laboratory that studies cellular organelles to see how experiments we discuss in class are performed in the laboratory.

7.343 The Microbiome and Drug Delivery: Cross-species Communication in Health and Disease
Instructor: Miguel Jimenez (jmiguelj@mit.edu, 949-285-0318, laboratory of Robert Langer)
Spring 2019. Thursdays, 11 pm – 1 pm. (Class day and time are flexible.) Room 68-150.

Are humans superorganisms? There are more microbes permanently living in our gut than there are human cells in our bodies. This rich community of bacteria, fungi and viruses, called the microbiome, plays a central role in human health and disease. Recent research has linked this passenger community to nutrition, circadian rhythms, infectious disease, inflammatory disease, cancer, diabetes, arthritis and even immune system and nervous system development. The connections seem to be so far-reaching that some scientists are starting to consider this human-microbiome system as a "holobiont" or "superorganism." Why are we realizing this situation only now? Are microbes actually interacting with us so fundamentally? What are the mechanisms by which effects of the microbiome are mediated? Could we survive without our microbiome? How can we analyze such a complex system? Can we exploit the microbiome to improve human health? Can interactions with microbes be harnessed for drug delivery? In this course, we will explore the primary scientific literature to find answers to these questions and to learn to critically assess observational and experimental data and distinguish between correlation and causality. We will discuss several of the key signaling molecules that mediate the interactions between humans and their microbiomes, such as human-produced antimicrobial peptides, microbial pheromones, bacterial peptide toxins and neuroactive microbial metabolites. We will learn about recent methods that make possible the analysis of these interactions. We will learn about such cutting-edge technologies as next-generation DNA and RNA sequencing and the use of germ-free mice. In addition, we will discuss how a large reduction in the cost of DNA synthesis is enabling the development of synthetic microbes that can be used to interrogate and manipulate the microbiome. Together these mechanistic insights and emerging tools are transforming microbiome research and might lead to new types of therapeutics and drug delivery for improving human health.

7.344 One at a Time - A Single-molecule and Single-cell View of the Foundations of Gene Expression
Instructors: Jean-Marie Swiecicki (jmsd@mit.edu, 617-253-1834, laboratory of Barbara Imperiali)
Lydia Herzel (herzel@mit.edu, 203-584-6345, laboratory of Gene-Wei Li)
Spring 2019. Thursdays, 1 pm - 3 pm. (Class day and time are flexible.) Room 68-150.

Every cell needs to read out the information stored in its genome. Even before the molecular machineries responsible for this process had been identified, Francis Crick, who received the Nobel Prize together with James Watson and Maurice Wilkins for their discovery of the structure of DNA, postulated that there is one underlying principle of gene expression, which he called The Central Dogma of Molecular Biology – genetic information is transcribed from DNA into RNA and subsequently translated into protein. The Central Dogma long provided the framework for the understanding of the processes of molecular biology. However, aspects of The Central Dogma have been challenged in multiple ways, e.g. upon the discovery of RNA viruses that can make DNA from RNA. Furthermore, the historical views of gene expression obtained from studies of populations of cells might not simplistically reflect how single cells express their information, an issue that could be especially important in the process of embryogenesis during which a few cells give rise to a whole organism. More specifically, averages need not indicate what goes on at the individual level, e.g., consider the "average" human with one ovary and one

testis. In this course we will explore insights gained when single-molecule and single-cell methods have been used to examine the transfer of information within individual cells. Focusing on the processes of transcription, pre-mRNA splicing, RNA decay and translation, we will seek answers to such questions as: What are the dynamics of transcription at the single-cell level compared to the level of a population of cells? Gene expression machineries are spatially organized, even within tiny bacterial cells. How does this organization affect the synthesis of proteins? How can synthetic biologists engineer transcriptional networks to generate cells with precise temporal oscillations that robustly recapitulate oscillating biological processes, e.g. circadian rhythm? By the end of this course students should be able to (1) recognize how single-molecule imaging, single-cell proteome- and transcriptome-analysis tools and (cryo-)electron microscopy led to a quantitative description of the processes defined by The Central Dogma, (2) describe how strategies for the regulation of gene expression are utilized both *in vivo* and in synthetic biology, (3) assess the applicability single-molecule and single-cell methods to their own biological problems of interest, and, most importantly, (4) be capable of critiquing the primary research literature and generate testable hypotheses from primary data. To illustrate the methods and concepts we discuss, we will take a field trip to an academic laboratory, where we will have the opportunity to observe directly how super-resolution movies are acquired and analyzed to study transcription.