Advanced Undergraduate Seminars
2015-2016

Fall 2015

7.341 The Highways of the Cell: The Intracellular Sorting Machinery and Its Involvement in Disease

Instructor: Raïssa Eluère (raissae@mit.edu, 410-330-9115, laboratory of Chris Kaiser)
Fall 2015. Tuesdays 11 am - 1 pm. (Class day and time are flexible.) Room 68-150.

In eukaryotic cells, cellular functions are performed in specific compartments called organelles. For example, DNA is replicated and transcribed in the nucleus, membrane proteins are degraded in the lysosome, and ATP is generated in the mitochondria. This compartmentalization of activities optimizes cellular functions but requires more complex mechanisms of intracellular signaling and transport than used by prokaryotic organisms. For example, in neurons neurotransmitters are delivered to specific locations (synapses) at the ends of axons. How can different molecules have different specific localizations within and outside cells? How can different molecules be secreted at different times and different places? The intracellular sorting machinery, which consists of a large set of protein complexes and is attached to the membranes of vesicles as well as to the plasma membrane, controls the transport of vesicles between organelles and between organelles and the plasma membrane. These protein complexes are conserved from yeast to human and are specialized for different aspects of the transport process. These complexes can also be the targets of bacterial toxins and viruses, and mutations that affect these complexes can cause disease. For example, the SNARE (SNAP REceptor) proteins mediate the fusion of vesicles with their target membranes and are themselves the target of the botulinum and tetanus bacterial toxins. The ESCRT (Endosomal Sorting Complexes Required for Transport) machinery enables a unique mode of membrane remodeling that results in the budding of membranes away from the cytoplasm. This process is required for the formation of the MVB (MultiVesicular Body) precursor organelle of the lysosome and, interestingly, for the budding of the HIV from the infected host cells. In addition, the neurodegenerative disorder FTD (FrontoTemporal Dementia) can be caused by mutations in the *CHMP2B* gene, which encodes a component of ESCRT complex. The analysis of the intracellular transport system has resulted in four Nobel Prizes between 1970 and 2013 and remains an area of extremely active research. In this course we will discuss past and present experiments that have allowed researchers to discover the cell's sorting machineries, how they are used by pathogens and their involvement in disease. The main goal will be for students to learn how to read and critically interpret the primary scientific literature. This course will provide exposure to a broad range of scientific approaches, including genetics, biochemistry, cell biology and high-resolution microscopy, and their applications in studies of a broad variety of organisms, including yeast, *Drosophila*, mouse and human. Students will visit a research laboratory using advanced live cell imaging tools for the study of the cell's sorting machinery.

7.342 Cancer Metabolism: How Hijacked Metabolic Pathways Support Tumor Growth
Instructors: Caroline Lewis (lewisca@mit.edu, 5-4523; laboratory of Matthew Vander Heiden)
Lucas Sullivan (lucasbs@mit.edu, 5-4523; laboratory of Matthew Vander Heiden)
Fall 2015. Tuesdays, 1 pm – 3 pm. (Day and class time are flexible.) Room 68-150.

Cellular metabolism is frequently considered to be a thoroughly understood process by which cells extract energy from nutrients to make adenosine triphosphate (ATP). For example, it is broadly known that cells oxidize glucose by glycolysis and the tricarboxylic acid (TCA) cycle to produce ATP by glycolysis and electron transport chain supported oxidative phosphorylation. However, while the foundations of cellular metabolism have been understood for over 50 years, recent discoveries have shown that metabolism is more than just synthesizing ATP. Disease states such as diabetes, hypoxia and cancer have all been shown to display drastic differences in cellular metabolism. Cancer cells specifically display what is known as the "Warburg Effect," the increased uptake of glucose and fermentation to lactate. In humans, glucose fermentation to lactate, an ATP inefficient process, is typically considered to occur exclusively in low oxygen conditions, such as in exercising muscle. Why cancer cells would forfeit so much potential ATP by bypassing the electron transport chain and excreting lactate is one of many fascinating questions that have arisen from a recent renaissance in metabolism research. New research has shown many conventional aspects of metabolism to be much more dynamic and malleable than previously recognized. This class will address several interesting questions related to metabolism research, such as: How can a single mutation in a TCA cycle enzyme create a new metabolite to cause cancer? How does a diabetes drug decrease cancer incidence and death? Do antioxidants prevent disease, or increase it? How does activation of cancer-associated genes rewire the metabolism of a cell? We will investigate these questions and other current topics in cellular and organismal metabolism. In addition, we will discuss current research methods and learn how to critically evaluate the experimental designs used in studies in this field. We will also visit a local pharmaceutical company that is targeting recent advances in cancer metabolism to revolutionize cancer therapy.

7.343 Unraveling the Molecular Mechanisms of Aging and Age-Related Diseases
Instructor: Caitlin Ondracek (ondracek@mit.edu, 3-0809, laboratory of Leonard Guarente)
Fall 2015. Wednesdays 11 am – 1 pm. (Class day and time are flexible.) Room 68-150.

Biological aging is associated with a time-dependent decline in function. While everyone is familiar with the aging process, the mechanisms responsible for aging and age-related disease have yet to be fully elucidated. Did you know that Bama, a remote village in China, has the most active Centenarians (people at least 100 years old) living today? Why does Japan have the longest average lifespan expectancies in the world? Why does the average lifespan vary from species to species? Why do some breeds of dogs have lifespans of over 15 years, while others have lifespans of about seven years? Why do naked mole rats outlive other rodent species by more than 20 years? Why are older people more likely to experience diseases like cancer, stroke, and Alzheimer's disease? By studying the aging process, scientists hope to gain a mechanistic understanding of aging. In this course, we will explore the scientific discoveries that have led to revelations about the molecular and cellular biology of aging. We will discuss how different model organisms -- including yeast, the nematode *C. elegans*, naked mole rats and dwarf mice --

are used to study aging. Several cutting-edge technologies frequently used in the field of the biology of aging will be explored, including gene microarrays, nucleic acid sequencing, and computer modeling. We will address key questions in this field, such as: Is aging a result of or the cause of disease? Can we intervene to stop or reduce the aging process? We will discuss the connection between aging and several diseases, such as cancer and neurodegenerative disorders, including Alzheimer's and Huntington's diseases. Studies in the field of aging have led scientists to speculate that an "elixir of life" might prolong health span. During our discussion of potential pharmacological therapeutics with anti-aging properties, we will learn about two compounds – one found in red wine, called resveratrol, and another originally identified as an anti-fungal medication, rapamycin. We will also discuss how lifestyle and dietary regimens, such as calorie-restriction, can intervene in aging and age-related diseases. We will explore how new interventions might be designed to target the processes involved in aging. The class will attend a meeting of the Boston Area Aging Data Club, where we will meet the authors of some of the research papers that will be discussed in class. We will hear presentations by scientists actively working on exciting and novel topics in the field of aging. This class will be focused on learning to read, critique and effectively interpret the primary scientific literature. Students should be able to identify experimentally tractable interesting biological problems and design experimental approaches by the end of this course, while learning about important techniques in the field of aging.

7.344 The Non-coding RNA Revolution: Short and Long Non-coding RNAs that Regulate Gene Expression

Instructors: Katrin Heindl (heindl@wi.mit.edu, 617-258-5990); laboratory of David Bartel
Marko Knoll (knoll@wi.mit.edu, 617-253-0377); laboratory of Harvey Lodish

Fall 2015. Wednesdays, 1 pm – 3 pm. (Class day and time are flexible.) Room 68-150.

Until recently, the vast majority of the mammalian genome was commonly regarded as functionally inert. The 20,000 protein-coding genes and the genes for known non-coding RNAs (rRNAs, tRNAs, snoRNAs) together accounted for no more than 25% of the genome, separated by large stretches of highly repetitive, apparently transcriptionally silent sequence referred to as "junk DNA." Over the past decade, new technologies such as microarray hybridization and next-generation DNA sequencing have enabled a thorough examination of entire transcriptomes (transcriptome, the total set of transcribed RNAs in a cell), uncovering a level of complexity far greater than expected. Now we understand that a substantial portion of the genome is transcribed, giving rise to an abundance of non-coding transcripts that mediate a diversity of unprecedented functions in gene regulation, including the establishment of repressive chromatin marks and sequence-specific silencing of messenger RNAs. In this class we will examine the modern techniques that have accelerated the field of non-coding RNAs, in particular next-generation sequencing. Focusing on the primary research literature, we will reconstruct the path from the implementation of these novel techniques to the analysis and integration of the data, arriving at the groundbreaking discovery of novel major classes of non-coding RNAs, such as microRNAs and lncRNAs (long non-coding RNAs). In humans, more than 60% of protein-coding genes are regulated by microRNAs, small non-coding RNAs that repress messenger RNAs based on sequence. Non-coding RNAs have been found especially important during development. During zebrafish morphogenesis, for example, one microRNA clears several hundred maternal

messenger RNAs that were passed on to the embryo by the mother and drives the embryo into the next stage of development. The most famous lncRNA, Xist, orchestrates the inactivation of one of the two X chromosomes in female mammals to equalize expression levels of X-encoded genes between females and males. In this class, we will explore the structural and functional diversity of non-coding RNAs, which have been implicated in modulating all stages of gene expression: establishment of chromatin states, transcription, translation, and mRNA stability. We will also discuss the roles of non-coding RNAs in diseases, such as cancer, in which the expression profiles of microRNAs are often dysregulated. Because microRNAs have varying expression patterns across different normal and pathological conditions, they are being used in molecular diagnostic tests for disorders as diverse as cancers, autoimmune diseases and infections. The class will visit a microRNA research laboratory and hear about challenges researchers must address in generating and analyzing microRNA data. This course aims to generate a deeper understanding of the biology of non-coding RNAs and teach students to critically read and interpret data in primary research papers. Students will be challenged to strengthen their critical thinking and analytical skills as well as their ability to think creatively and flexibly.

7.345 The War on Superbugs -- Antibiotic Development and the Emergence of Drug-Resistant Bacteria

Instructors: Julie Silverman (silverjm@mit.edu, 617-253-1834, laboratory of Barbara Imperiali)
Monika Musial-Siwek (monikam@mit.edu, 617-253-0206, laboratory of Barbara Imperiali)

Fall 2015. Wednesday, 3 pm - 5 pm. (Class day and time are flexible.) Room 68-150.

Bacteria and fungi produced antibiotics, small molecules that can prevent the growth of or kill bacteria by inhibiting essential biological pathways, as a defense mechanism long before humans walked the earth. The discovery of antibiotics and their implementation in the clinic radically changed modern medicine, saving countless lives by treating infections that were once difficult to cure, such as syphilis, strep throat and tuberculosis. Although antibiotics were once referred to as the "wonder drug" of modern medicine, a growing number of drug-resistant bacteria have emerged since the beginning of the 20th century, which has compromised their effectiveness. Furthermore, as a consequence of the introduction of diverse antibiotics, multi-drug resistant bacteria have emerged, negating recent advances in eradicating bacterial infections across the globe. Scientists have successfully studied the origins of many drug-resistant bacteria, shedding light on the molecular mechanisms bacteria have evolved to persist in the presence of antibiotics. Understanding these pathways will be fundamental for the future of medicine. During this course, we will discuss many aspects of antibiotics, including techniques used to discovery these compounds, their modes of action and uses in medicine. For example, we will learn how penicillin and vancomycin were discovered. We will discuss antibiotic-resistant bacteria and the molecular mechanisms underlying resistance, including horizontal gene transfer, point mutations and efflux pumps. Additionally, we will learn about pioneering work to treat infections with engineered antimicrobial peptides and microbiome replacement therapies. The course will focus on the primary research literature, and we will learn about practical laboratory techniques, experimental design and how to interpret data and critique conclusions offered by authors. Students will have the opportunity to visit a local hospital to learn about how patients are treated

with antibiotics and what is being done to attempt to avoid the continuing emergence of antibiotic resistance.

7.346 Law and Order: Genetic and Epigenetic Control during Hematopoiesis

Instructors: Sherry Lee (hsylee@wi.mit.edu, 8-3077; laboratory of Harvey Lodish)
Xiaofei Gao (xgao@wi.mit.edu, 8-3077; laboratory of Harvey Lodish)

Fall 2015. Thursdays, 11 am – 1 pm. (Class day and time are flexible.) Room 68-150.

Mammalian blood contains more than ten distinct cell types, all of which are generated from a single precursor cell type — the hematopoietic stem cell (HSC). Blood is a tissue with enormous regenerative capacity. Under normal conditions, our body produces 2 to 3 million erythrocytes (red blood cells) per second to transport oxygen in exchange for carbon dioxide. In one microliter of our blood, there are up to 450,000 platelets, which are generated from megakaryocytes and function to prevent bleeding and minimize blood vessel injury. There are also 4,000 to 10,000 white blood cells per microliter of our blood, including neutrophils, lymphocytes, basophils, monocytes, eosinophils and others, all of which are specialized cell types involved in innate and acquired immunity. HSCs reside at the top of the pyramid of the hematopoietic cell hierarchy and constantly must decide between quiescence and division and between self-renewal (replicating themselves) and differentiation (becoming progenitors of specific cell types). The DNA sequence in almost all cells of an individual is identical, and how gene expression programs are precisely established in different cells at distinct stages of hematopoiesis remains an intriguing and important question. Multiple transcription factors (which regulate gene expression via sequence-specific DNA binding) and epigenetic regulators (which regulate gene expression via modulating chromatin state) are essential in controlling these developmental processes. The level of each of these factors is normally strictly regulated at each stage of hematopoiesis. Aberrant expression of any of these factors, because of mutations or environmental influences, often leads to diseased states. For instance, mutations of KLF-1 (Krüppel-like factor-1), a transcription factor critical for erythropoiesis, can lead to congenital dyserythropoietic anemia type IV (CDA-IV); mutations of EZH2 (Enhancer of zeste homolog 2), an enzyme that methylates histones, can result in myelodysplastic syndromes (MDS), which are a heterogenous group of hematologic malignancies characterized by clonal expansion of bone marrow myeloid cells with impaired differentiation; long-term benzene exposure will alter DNA methylation state, change the expression of certain genes involved in carcinogenesis and eventually cause leukemia or other blood cancers. In this course, we will learn to read, critique and interpret data from the primary research literature, focusing on 1) how HSCs make decisions to become different specific cell types; 2) the epigenetic regulators required for generating each cell type; 3) diseases related to abnormal expression of these epigenetic regulators, and 4) current progress in developing treatments for epigenetic diseases. Both classic and brand new experimental methodologies in stem cell and molecular cell biology will be discussed. We will have a field trip to biotechnology companies Acceleron Pharma, which is developing therapeutics for thalassemia and Diamond-Blackfan anemia (DBA) and Rubius Therapeutics, a biotechnology company developing engineered red blood cells for diagnostics and therapeutics.

7.347 Living Dangerously: How the Immune System Maintains Peace with Trillions of Commensal Bacteria while Preventing Pathogenic Invasion

Instructors: Matthias Truttmann (truttman@wi.mit.edu, 617-501-9327, laboratory of Hidde Ploegh)
Angelina Bilate (abilate@wi.mit.edu, 917-843-0154, laboratory of Hidde Ploegh)

Fall 2015. Thursdays, 1 pm – 3 pm. (Class day and time are flexible.) Room 68-150.

In humans, the mucosal epithelia that line the gastrointestinal, urogenital and respiratory tracts are important routes of entry for bacterial pathogen invasion. At the same time, mucosal surfaces are colonized by many harmless bacteria, the so-called commensals or microbiota. Not only are these commensals well-tolerated and non-pathogenic, but also they are in fact essential for diverse body functions, such as nutrient absorption and synthesis of vitamins (biotin and vitamin K). Interestingly, most of us do not develop a strong immune response against commensals (or, similarly, against the food we eat every day). This striking specificity of recognition reflects the tight regulation of the immune system at mucosal surfaces to maintain a balance between tolerogenic and effector immune responses. In this course, we will examine how the immune system acts to destroy pathogenic invaders while tolerating colonization by necessary commensal bacteria. As a counterpoint, we will also explore sophisticated strategies that help some bacteria evade our immune system. Did you know that the intestinal mucosa is considered to be always "physiologically inflamed," because of its daily exposure to, and activation by, foreign antigens? Or that sub-populations of certain pathogenic bacteria employ suicidal strategies to promote surface colonization? These and many more interesting aspects of host-commensal / host-pathogen interactions will be introduced and analyzed. We will critically review the primary research literature and systematically discuss the experimental data, leading us to either concur with or challenge published analyses and conclusions. We shall ask questions such as: Are there additional controls that are essential to validate the interpretations? Are there further experiments that would have strengthened the conclusions? What experiment would you do next if this study were your responsibility? Such questions will help direct our discussions beyond the confines of the research paper being discussed. We hope that this course will excite students to join the next generation of scientists who explore the intersection of host-pathogen interactions and immunology.

7.348 Of Mice and Men: Humanized Mice in Cancer Research

Instructor: Mandeep Kaur (mkaur@mit.edu, 4-5100, laboratory of Jianzhu Chen)

Fall 2015. Thursdays 3 pm – 5 pm. (Class day and time are flexible.) Room 68-150.

Almost everyone knows someone whose life has been affected by cancer. This devastating disease, which continues to carry a social stigma in certain parts of the world, generally remains unbeatable, despite numerous efforts to develop anti-cancer therapies since the inception of the War On Cancer in the 1970s. Why is cancer such a difficult disease to treat? Despite all the effort and money poured into developing new cancer treatments, why are there so few cancer therapies that specifically target tumor cells? What is the best system to model the development of a human tumor? How can novel therapies be tested in a system that mimics the human body by modeling the interaction between human tumor cells and the human immune system, which plays a crucial role in the detection and elimination of tumor cells? Cancer is thought to develop

and spread by escaping surveillance from human immune cells, which would otherwise eliminate the disease. How can new treatment modalities, especially immune-based therapies that harness the natural ability of immune cells to kill target cells, be developed to treat cancer? These and other questions will be addressed in this course. We will explore the concepts of mouse models for human cancer, humanized cancer mice and cancer immunotherapy by reading recent and classic research articles. Humanized mice, like Mouse Man from the comic world, are essentially mice on the outside and human in the inside, because of the presence of an intact and functional human immune system after engraftment with human stem cells. In humanized cancer mice the development of a human tumor occurs in the context of a normal human immune system, hopefully mirroring the situation in patients. We will focus on analyzing and critiquing research papers describing the development of human cancer models using humanized mice. Students will learn to focus on experimental design and interpretation when reading the research literature. This focus will guide discussions about the strengths and weaknesses of humanized mice (also referred to as humice) in cancer research and the unique position such models have as a platform for the testing of new therapies prior to use in the clinic. The course will end with an exploration of a tantalizing new concept: the development of "personalized mice" or mouse "avatars" for individual cancer patients to test drug toxicities prior to dosing the patient as an effort to improve therapeutic efficacy and minimize undesired side effects. Many believe that immunotherapies represent the future of cancer therapy and humanized mice are a recent addition to the cancer biologist's tool-kit for modeling human cancer. This course will introduce the latest developments in the fields of cancer biology and immunotherapy. We will use the humice cancer field as a vehicle to fulfill the primary objective of this course -- the art and science of reading, analyzing and critiquing research articles. We will also attend one or more seminars by experts in the field and visit a research laboratory actively involved in the generation and study of cancer humice.

Spring 2015

7.341 Treating Infertility – From Bench to Bedside and Bedside to Bench

Instructors: Michelle Carmell (carmell@wi.mit.edu, 617-258-5174; laboratory of David Page)
Jana Hersch (jckoubov@mit.edu, 617-710-3496, Educational Coordinator, MIT Biology)

Spring 2016. Tuesdays 1-3 pm. (Class day and time are flexible.) Room 68-150.

In the western world, approximately 10-15% of couples suffer from subfertility. Consequently, over 5 million babies have been born thanks to assisted reproductive technologies, and more than half of those have been born in the past six years. In some countries, 3-5% of births are achieved with assisted reproductive technologies, and this number is projected to grow as societies become increasingly interested in beating the biological clock. This class will discuss the basic biology behind fertility and explore the etiology of infertility. We will cover the latest developments in reproductive science and consider the clinical challenges of translating research findings into medical treatments. We will discuss recent studies of gonadal stem cells and their use for rejuvenation of fertility, oocyte and embryo cryopreservation studies and usage, current diagnostic tools for common causes of male infertility, and key mouse models with reproductive

phenotypes. This class will highlight open questions in reproductive biology, familiarize students with both tried-and-true and emerging reproductive technologies, and explore the advantages and pitfalls of each. Students will have the opportunity to visit a Boston-area IVF (*in vitro* fertilization) clinic and speak with researchers who are on the front lines of reproductive technologies.

7.342 Pluripotent Stem Cells and Genome Engineering for Modeling Human Diseases

Instructors: Malkiel Cohen (malkiel@wi.mit.edu, (617)852-5860, laboratory of Rudolf Jaenisch)
Katherine Wert (wert@wi.mit.edu, (425)922-9055, laboratory of Rudolf Jaenisch)

MIT OpenCourseWare Website:
http://ocw.mit.edu/courses/biology/7-342-pluripotent-stem-cells-and-genome-engineering-for-modeling-human-diseases-spring-2015/index.htm

Spring 2016. Tuesdays, 3 pm – 5 pm. (Class day and time are flexible.) Room 68-150.

One of the major priorities in biomedical research is understanding the molecular events that establish the complex processes involved in human development and the relationships of these processes to human disease and disease progression. The role of stem cells as a tool to help reveal these processes has long been appreciated. During the 20th century, Mario Capecchi, Martin Evans, and Olivier Smithies made ground-breaking discoveries using mouse embryonic stem cells for gene targeting in mammals. Their efforts made it possible to modify DNA of specific genes within the genomes of living and fertile mice, allowing scientists to determine the roles of individual genes in health and disease. This approach of genome engineering has produced numerous non-human vertebrate models of human disorders, including diabetes, cancer, cardiovascular and neurodegenerative diseases. For their discoveries, Capecchi, Evans, and Smithies shared the 2007 Nobel Prize in Physiology and Medicine. In 2012, the Nobel Prize in Physiology and Medicine was received by Shinya Yamanaka and John Gurdon for their discovery that cells of mature humans and other animals can be reprogrammed to an early embryonic stage, known as pluripotency, and then differentiate into various cell types of the adult body. This work and many other studies have stimulated the stem cell field into generating pluripotent stem cells from human patients, and these patient-specific stem cells have been used to better model human diseases by reflecting those disorders in a cell culture system. Scientists can now cause such patient-specific stem cells to differentiate into the cell type that is affected by the disease, allowing the study of the diseased cells and an understanding of the mechanisms underlying disease progression; these cells can be further used to test potential treatment options. In this class, we will explore the field of stem cell biology and the way in which this field has developed and shaped our ability to study complex human disease. We will introduce the topics of stem cell biology and genome engineering through critical reading of both the classical and newest primary research literature. This course will focus on the methods behind the generation of embryonic and induced pluripotent stem cells, genome editing to create transgenic animal models of human diseases, regenerative medicine (such as the transplantation of stem cell-derived cell types to replace diseased tissues), and current hot topics in genome engineering such as CRISPR/cas9, a novel method that can be used to delete or insert genes of interest in cultured cells and intact organisms. In addition, this course will discuss specific disease model systems and their benefits/limitations for understanding the disease and treating human patients. Students will obtain a deep understanding of the main concepts and questions concerning stem cell

biology, become familiar with current research techniques to model complex human diseases, and learn to critically evaluate the experimental design and claims in this field.

7.343 An RNA Safari: Exploring the Surprising Diversity of Mammalian Transcriptomes

Instructors: Athma Pai (athma@mit.edu, 3-7039, laboratory of Chris Burge)
Matt Taliaferro (jmtali@mit.edu, 3-6726, laboratory of Chris Burge)

Spring 2016. Wednesdays, 11 am-1 pm. (Class day and time are flexible.) Room 68-150.

One of the most fascinating aspects of mammalian biology is the use of a single DNA blueprint to create a myriad of RNA molecules that define each differentiated cell type. For many years, it was thought that RNA exists solely to do the bidding of DNA by relaying instructions for protein synthesis to the cytoplasm and aiding in translational processes. However, recent research into RNA biology has shown that RNA exists in the cell in many varied forms, each with a distinct set of cellular responsibilities. We now understand that RNAs are dynamic molecules capable of participating in a wide range of chemical reactions, from guiding the modification and processing of other RNA molecules to directing protein complex formation or silencing unwanted transposon expression. Many newly discovered RNA classes have unique capabilities and reveal surprising complexity in their compositions, lengths, and even shapes. The aim of this class is introduce the exciting and often underappreciated discoveries in RNA biology by exploring the diversity of RNAs – encompassing classical molecules such as ribosomal RNAs (rRNAs), transfer RNAs (tRNAs) and messenger RNAs (mRNAs) as well as newer species, such as microRNAs (miRNAs), long-noncoding RNAs (lncRNAs), and circular RNAs (circRNAs). For each class of RNA we will discuss its role as a critical component of cellular machinery, its function in the context of disease, and/or its adaptation as a powerful tool in molecular biology. We will discuss the seminal studies that led to the discovery of each class of RNA, beginning with classic experiments that first identified the mRNAs, rRNAs and tRNAs as key regulators of gene expression. Given this historical perspective, we will move forward by discussing a new class of RNAs each week. As we progress, we will consider advances in techniques and equipment that have that facilitated the discovery, annotation, and analysis of new RNA molecules, with a particular focus on high-throughput sequencing and novel genomic methods. In line with this approach, we will visit a research platform at the Broad Institute of MIT and Harvard to better understand the impact of these techniques and to meet scientists helping to further discoveries in RNA biology. Class sessions will be highly interactive and focus on the critical reading of the primary research literature to introduce important concepts in RNA biology, experimental approaches, and as-yet-unanswered questions in the field. For each new class of RNA, we will evaluate the evidence for its existence as well as for its proposed function. Students will develop both a deep understanding of the field of RNA biology and the ability to critically assess new papers in this fast-paced field.

7.344 Modulating DNA Damage Tolerance Pathways as an Approach to Novel Cancer Therapeutics

Instructor: Kinrin Yamanaka (kinrin@mit.edu 617-253-3745; laboratory of Graham Walker)
Spring 2016. Wednesdays, 1 pm – 3 pm. (Class day and time are flexible.) Room 68-150.

Genomic DNA is constantly under attack by a wide variety of DNA-damaging agents, and DNA mutations can cause cancer. Although cells possess multiple DNA repair mechanisms, DNA lesions can escape repair, and DNA synthesis can be blocked as a consequence. Translesion DNA synthesis (TLS) is a mechanism that helps cells tolerate unrepaired DNA lesions through replication of damaged DNA by TLS DNA polymerases. The outcome of the lesion bypass can be either accurate or mutagenic, depending on the identity of the TLS polymerase involved and the type of DNA lesion. Thus, on the one hand TLS polymerases can prevent cancer by catalyzing accurate replication bypass of specific DNA lesions and performing DNA repair synthesis. For example, TLS polymerase h accurately bypasses thymine dimers, the major ultraviolet light-induced DNA lesions, and deficiency in this polymerase causes Xeroderma Pigmentosum Variant XP-V, a disorder associated with a high incidence of skin cancer in humans. However, on the other hand, TLS polymerases upon encountering different DNA substrates also can promote carcinogenesis and chemoresistance by introducing mutations in genes during error-prone TLS or when performing TLS past DNA lesions induced by chemotherapeutic agents. In this case, TLS polymerase h can facilitate cellular resistance to commonly used chemotherapeutic agents, such as cisplatin by catalyzing replication bypass of cisplatin-induced lesions. In this course, we will first discuss the basic mechanisms of tumorigenesis and chemoresistance. We will then turn our focus to TLS pathways and review the functions of TLS polymerases and discuss how defects in and/or dysregulation of the functions of TLS polymerases can promote tumorigenesis and chemoresistance. Additionally, we will learn about the emerging cancer therapies that target TLS pathways. Toward the end of the course, we will discuss the roles TLS polymerases play outside TLS and how these previously unknown functions of TLS polymerases relate to tumorigenesis and chemoresistance. We will discuss the primary research literature to allow students to learn how to read and critique research papers. There will also be an opportunity to visit a local pharmaceutical company that is developing cancer therapeutics.

7.345 Are There Inherent Limits to Our Understanding in Biology? A Challenge and Exploration Based on Diseases of the Nervous System

Instructor: Sepehr Ehsani (ehsani@csail.mit.edu; 617-797-8940; laboratory of Bonnie Berger)
Spring 2016. Wednesdays 3 pm – 5 pm. (Class day and time are flexible.) Room 68-150.

Molecular biology over the past two decades has experienced significant changes in both methods and understanding, with major technical innovations facilitating diverse breakthroughs. For example, high-throughput techniques and genome sequencing, introduced in the 1990s, have generated vast quantities of data and valuable insights concerning the workings of the cell under normal and disease conditions. The impact of these findings in the context of human disease has been greatest in the case of single-gene disorders (e.g., cystic fibrosis), which in general are relatively rare. However, most common human diseases, ranging from solid tumors (e.g., sarcomas and carcinomas) to cardiovascular, neurodegenerative and neuropsychiatric

pathologies, have remained refractory to non-symptomatic therapeutic interventions, mostly because researchers have been unable to identify simple causative mechanisms. In other words, most common diseases have proved to be both heterogeneous in origin and mechanistically complex. Why is this the case, and what is preventing us from reaching an understanding of the pathologies of these disorders -- a scientific understanding that is not merely descriptive but rather founded on mechanism? This course aims to examine current challenges in the field of pathobiology (the study of the molecular and physiological mechanisms of disease). Students will discuss, through detailed analysis of the primary research literature, whether these challenges possess an underlying commonality. For example, have ultimate causes of many diseases remained elusive because of (i) limitations in experimental or computational methodology, (ii) limitations in our ability to interpret complex data, and/or (iii) some unknown facet of the diseases themselves? Can we identify a common thread in the answers to these questions for multiple diseases? In our efforts to answer such questions, might we discover some inherent limitation to human understanding -- a cognitive limitation similar to that which a rodent faces when fruitlessly attempting to learn to navigate a prime-number maze? If the answer is yes, can we do anything to overcome that limitation? If the answer is no, does that mean that there are no upper limits to what science can reveal and to what we can comprehend, e.g., concerning the etiology of a disease? We will focus on disorders of the nervous system, such as neurodegenerative diseases and cancers of the central nervous system. Our discussions will be framed by two general themes: (i) the quantification and meaning of uncertainty in experimental biology and (ii) a potential limit to scientific understanding. The primary goals of this course are for students to enhance their skills in critically evaluating the primary research literature and to think about the relationship between objective realities as typified by experimental data and human cognitive abilities and limits. The course will include a field trip to a computational/theoretical biology laboratory focused on the structures of proteins to observe how theoretical studies of protein structures can help reveal novel facets of pathological protein-protein interactions in neurodegenerative disorders.

7.346 Engineering Immune Responses through Biomaterial Design

Instructors: Tyson Moyer (tmoyer@mit.edu, 3-0656, laboratory of Darrell Irvine)
Kavya Rakhra (kavyarakhra@gmail.com, 3-0656, laboratory of Darrell Irvine)

Spring 2016. Thursdays, 11 am – 1 pm. (Class day and time are flexible.) Room 68-150.

Vaccines are combinations of antigens (substances that stimulates an adaptive immune response) and adjuvants (substances that accelerate, prolong or enhance an antigen-specific immune response) that can elicit a robust, long-lasting immune response. Vaccines have been used to eradicate diseases like small pox and polio. Other diseases, including HIV, cancer, and various autoimmune disorders, have not been able to be effectively treated using vaccines. In this course we will focus on bioengineering approaches to better understand the mechanisms of immune responses and to create novel therapeutics. Based upon the recent primary research literature, we will discuss approaches to understand and enhance the interactions of synthetic biomaterials with the immune system to program immune cells to perform specific tasks, such as the production of HIV-neutralizing antibodies by B cells or the elimination of cancer cells by enhancing the activity of cytotoxic T cells. Specifically, we will discuss parameters that affect the behaviors of different materials, such as particle size, shape, and chemical structure, in the contexts of

vaccines. We will also consider other immunotherapies, such as the engineering and delivery of anti-tumor antigen specific T-cells. For effective vaccine design, antigens and specific immune-cell targeting molecules (e.g. antibodies specific to surface receptors on immune cells) must be displayed on the surface of larger particulates or scaffolds. Additionally, immunostimulatory danger signals that indicate the presence of pathogens to and trigger responses from the innate immune system must be hidden and encapsulated into the interior of the material scaffold. The effects of materials properties on vaccine performance will be discussed in the context of the route of administration, the trafficking of particles within the body, and the release of antigens. We will critically examine the functioning of the immune system in normal and diseased states such as cancer, autoimmune disorders and HIV/AIDS as well as other infectious diseases. We will discuss strategies to optimize biomaterials vaccine design through controlled release of antigens and adjuvants using different materials platforms (polymers, lipids, metals). We will visit a biotechnology company that focuses on the synthesis of lipid-based materials to design therapeutic vaccines to treat human papilloma virus (HPV) induced cancers. Students will gain an understanding of the biological and synthetic parameters that are important in materials design for the modulation of the immune system as well as the ability to evaluate and design well-controlled experiments to test scientific hypotheses.

7.347 Peptides as Biological Signaling Molecules and Novel Drugs
Instructor: Mohammed Shabab (shabab@mit.edu, 617-253-3745, laboratory of Graham Walker)
Spring 2016. Thursdays, 1 pm - 3 pm. (Class day and time are flexible.) Room 68-150.

All living cells possess the machinery for peptide synthesis, secretion, and posttranslational modifications. An enormous structural and functional diversity of peptides is generated by use of this cellular machinery. Peptides are broadly used as signal molecules for intercellular communication by prokaryotes, plants, fungi, and animals. Peptide signals in animals include vast numbers of peptide hormones, growth factors and neuropeptides. Some of the best known examples are enkephalins (which help us sense pain), somatotropin (which helps us grow), and insulin and glucagon (both of which regulate our blood glucose levels). Similarly in plants, peptide signals such as CLAVATA3 play important roles in development. Peptides are also used by living organisms as components of their host defense systems. What determines the functional specificity of each peptide? How do these small polymers of amino acids survive hostile protein-digesting enzymes? How are peptides able to communicate with their specific peptide receptors and other interacting proteins for proper function? In this course, we will learn about molecular bases of peptide signaling. In addition, peptides potentially can be used as potent broad-spectrum antibiotics and hence might define novel therapeutic agents. For example, antimicrobial peptides (AMPs) are low molecular weight proteins with broad spectrum antimicrobial activity against bacteria, viruses, and fungi and are found among all lifeforms. The ability of AMPSs to kill multidrug-resistant microorganisms has gained them considerable attention and clinical interest, since multidrug-resistant microorganisms have developed resistance to multiple antimicrobial agents and are difficult to treat with available antibiotics. One of the most notorious examples is MRSA, deadly strains of methicillin-resistant *Staphylococcus aureus*. Infections with these pathogenic bacteria are untreatable with known antibiotics like gentamicin, streptomycin and kanamycin**.** Some antimicrobial peptides can kill methicillin-resistant *S. aureus* strains, making these promising drugs or drug leads. In this class, we will discuss signaling and antimicrobial peptides, their biological functions, mechanisms of action, and applicability as therapeutic

agents. Students will learn about various human defense peptides, such as defensins, neuropeptides and about plant peptides involved in symbiosis, such as nodule-specific cysteine-rich peptides. We will consider techniques to detect, quantify and modify peptides. We will also discuss experimental methods, such as high-performance liquid chromatography (HPLC) and liquid chromatography coupled with mass spectroscopy (LC-MS), used for quantification of peptides and other small molecules. We will focus on the primary research literature, and students will learn how to read and critique research papers. Additionally, we will visit Aileron Therapeutics, a pharmaceutical company based in Cambridge, MA, which is developing peptide inhibitors of p53 pathways for treatment of solid and hematological malignancies.

7.348 An Evolutionary Arms Race: Molecular and Immunological Mechanisms Underlying the Causes of Infectious Diseases

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Infectious diseases were the leading cause of human death until just this past century, and continue to be so in low-income countries. The surge forward in the biological understanding of pathogens that began in the late 19th century led, with impressive speed, to the near eradication of the most deadly bacterial, viral, and parasitic afflictions in developed nations. Nevertheless, new infectious agents, such as HIV and SARS coronavirus, adapt to humans on a regular basis and challenge both our immune and healthcare systems. Modern tools now allow us to dissect in exquisite detail the mechanisms exploited by infectious agents that contribute to their propagation and, ultimately, to their morbidity and mortality in human populations. Understanding how pathogens invade a host, replicate by hijacking the host's cells, and evade the immune system requires an understanding of basic molecular and cell biology and the ability to apply the concepts of modern biology to new problems. In fact, studying host-pathogen interactions and using pathogens as biological probes have led to fundamental discoveries in the field of cell biology. In this course, students will learn to critically analyze the primary research literature and to understand, critique, interpret, and design scientific experiments in the field of host-pathogen interactions. The strategies used by the most successful human pathogens will be examined, with an emphasis on the molecular details of the pathogen life cycles that lead to morbidity and the countermeasures employed both by the immune system and by medical treatments to combat them. We will discuss well-studied pathogens for which effective treatments have long been available as well as emerging diseases that have only begun to be fully understood. The goals of this course are to challenge students to apply their basic knowledge about biology to the pathology of human infectious diseases and to attain a perspective concerning the challenges of addressing the substantial burden of infectious disease in less developed parts of the world. Students will visit a local academic laboratory focused on the elucidation of novel interactions between a human pathogen and host cells.