Advanced Undergraduate Seminars
2013-2014

Fall 2013

7.341 Unraveling the Molecular Mechanisms of Aging and Age-Related Diseases.
Instructors: Abhirup Das (abhirup@mit.edu, 3-3567, laboratory of Leonard Guarente)
Caitlin Ondracek (ondracek@mit.edu, 3-0809, laboratory of Leonard Guarente)
Fall 2013. Thursdays, 11 am- 1 pm. (Class date 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? How 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 to study aging will be explored, including gene microarrays, nucleic acid sequencing, and computer modeling. We will address key questions in the field of aging: 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.

7.342 Cell-material Crosstalk: Engineering Cell-Instructive Biomaterials
Instructors: Danya Lavin (dlavin@mit.edu, 3-3443) and Matthew Webber (mwebber@mit.edu; 8-0468) (laboratories of Robert Langer and Dan Anderson)
Fall 2013. Wednesdays, 11 am -1 pm. (Class time is flexible.) Room 68-150.

Biomaterials are substances that have been designed to direct the course of any therapeutic or diagnostic procedure by controlling interactions with biological systems. A large toolbox of non-biological materials has been engineered to study cell behavior at the cell-material interface. In this course, we will examine how this interface can be leveraged to study cellular systems and generate novel therapeutics. A critical evaluation of the primary research literature will be used to frame discussions about the interactions between cells and biomaterials. In particular, we will discuss how cell behavior can be altered by controlling biochemical and biophysical cues of substrate materials, how new organs and tissues can be produced by the use of structured scaffolds that direct cells into organized forms, and how specific patterning of materials can enable biological processes to be studied and altered at the single-cell level. We will also consider the applications at patterned cell-material interfaces to build artificial systems, such as organs-on-a-chip, which can be used to perform preclinical tests for the activity and toxicity of drug candidates. Also, we will discuss the combination of non-biological materials with genetic material (DNA and RNA), which can be a robust approach to modifying gene expression at the level of cells, tissues, or organs. We hope that your introduction to the cell-materials interface will inspire you to work at the intersection of biology and engineering and that you will help pioneer new and improved strategies to engineer this interface for functional applications.

7.343 Powerhouse Rules: The Role of Mitochondria in Human Diseases
Instructors: Dan Ferullo (ferullo@mit.edu, 3-3745; laboratory of Graham Walker)
Sanjay D'Souza (sdsouza@mit.edu, 3-3745; laboratory of Graham Walker)
Fall 2013. Wednesdays, 1 pm – 3 pm. (Class time is flexible.) Room 68-150.

In newspapers and textbooks, mitochondria are described as the "powerhouses" of life – tiny power generators inside living cells that produce virtually all the energy we need to live in the form of adenosine triphosphate (ATP). In addition to supplying cellular energy to eukaryotic cells, mitochondria are involved in a range of other critical processes, such as signaling, cellular differentiation, and cell death, as well as the control of the cell cycle and cell growth. While most of the estimated 2,000 proteins found in a mitochondrion are encoded by the nucleus, mitochondria house their own genome, called mtDNA. The human mitochondrial genome contains only 37 genes, of which 13 encode the proteins of the respiratory chain while the others encode mitochondria-specific translational machinery. Proper maintenance of mitochondria by eukaryotic cells is crucially important. A variety of clinical disorders involve molecular defects in mitochondrial function and mitochondrial quality control. For example, failure to clear out defective mitochondria by a process called "mitophagy" is a defect in some types of Parkinson's disease. Other neurodegenerative diseases have been shown to involve excessive

production of reactive oxygen species (ROS), a byproduct of mitochondrial respiration, which can lead to damage of DNA, RNA, proteins and lipids. Furthermore, mutations in mitochondrial DNA have been associated with promoting tumor growth and causing defects in apoptosis, also known as "programmed cell death," in cancer, thereby allowing cells that should die instead to survive and proliferate. In this class, we will learn about the importance of proper mitochondrial function in eukaryotic cells. We will also discuss the quality control mechanisms that protect cells from malfunctioning mitochondria. Lastly, we will learn about the molecular basis of defective mitochondria that have been identified in human diseases.

7.344 Issues of Commitment: The Hows and Whys of Stem Cells

Instructors: Mansi Srivastava (mansi@wi.mit.edu, 510-684-8693; laboratory of Peter Reddien)

Josien van Wolfswinkel (josien@wi.mit.edu, 4-2132; laboratory of Peter Reddien)

Fall 2013. Tuesdays, 11 am – 1 pm. (Class time is flexible.) Room 68-150.

Most animals begin life as a single cell: the fertilized egg, or zygote. The zygote is able to generate all other cells and tissues that later make up the adult organism. In many (but not all) animals, cells of the early embryo divide to generate cells all of which maintain the potential to make many, or even all, differentiated cell types. However, by the time the adult body plan is in place, most of the cells that make up the organism are unable to divide, and the remaining dividing cells are usually much more restricted in their fates. Nevertheless, most adult animals maintain some cells that are able to divide and self-renew. Such cells are referred to as adult stem cells. In the case of some animals, such as planarians (small non-parasitic flatworms), adult stem cells are able to replace essentially any type of tissue. These stem cells are therefore referred to as adult pluripotent stem cells. In the case of other animals, such as humans, adult stem cells have only highly limited potential: they are lineage-restricted stem cells and can generate only those cells that are closely related by cell lineage. Still other animals, such as nematodes (roundworms), have no adult somatic stem cells and maintain only germline stem cells, which have the potential to make all adult tissues in the next generation. In this course we will explore three main topics concerning animal stem cells. First, we will address what it means to be a stem cell. We will explore how molecular studies of adult stem cells in diverse animals ranging from jellyfish to humans are revealing essential and highly evolutionarily conserved molecular mechanisms related to the maintenance of stem-cell potency. Second, we will compare the features of adult stem cells to those of other multipotent cells, such as early embryonic cells, and discuss similarities and differences among multipotent cells at different stages of life. Third, we will evaluate how and why different animal groups have evolved the ability to maintain pluripotent vs. lineage-restricted adult stem cells. For example, we will consider why humans have evolved to maintain only lineage-restricted stem cells, given that pluripotent adult stem cells would appear to give so many advantages. We will explore these ideas through the critical reading of the primary literature, including both classical and very recent papers in stem cell biology. Students will obtain a deep understanding of the main concepts and

questions concerning stem cell biology, become familiar with current research methods in the field, and learn to evaluate critically the design of experiments used in these studies.

7.346 DNA Wars: How the Cell Strikes Back to Avoid Disease after Attacks on DNA

Instructors: Jennifer Jordan (jjjordan@mit.edu, 3-8096; laboratory of Leona Samson)
Zachary Nagel (znagel@mit.edu, 3-8096; laboratory of Leona Samson)
Fall 2013. Thursdays 1 pm – 3 pm (Class time is flexible.) Room 68-150.

A never-ending molecular war takes place in the nucleus of your cells, with DNA damage occurring at a rate of over 20,000 lesions per cell per day. Where does this damage come from, and what are its consequences? What differs in the molecular blueprint of individuals who can sustain attacks on DNA and remain healthy compared to those who become sick? Constant exposure to exogenous factors commonly found in food, water, air, and tobacco smoke as well as endogenous byproducts of metabolism can damage DNA. If left unrepaired, this damage can lead to various disorders, such as diabetes, premature aging, neurodegenerative disorders, and cancer. To preserve the integrity of the genome, our cells have evolved an elegant collaboration among multiple DNA repair pathways, which respond to specific DNA lesions, and checkpoints, which arrest the cell cycle to allow additional time for repair to proceed or to stimulate programmed cell death if the damage is too extensive. An individual's distinct genetic background influences the susceptibility of his or her cells to particular types of damage and their ability to process specific lesions. These differences can influence how cells from healthy individuals respond to damaging agents, which in turn can cause one individual to be more sensitive to a particular form of DNA damage than another. Thus, exposure to genotoxins that damage DNA, like the alkylating agent mustard gas, is dangerous because it can increase the susceptibility of cells to acquiring mutations that contribute to carcinogenesis and death. Counterintuitively, closely related chemicals like carmustine (also known as BCNU) are components of drug combinations used to treat cancer, and so genetic differences among individuals that influence pathways involved in the repair of DNA damage can play a role in responses to chemotherapeutic treatments. Additionally, individuals who harbor defects in a DNA repair pathway are generally more sensitive to the effects of DNA damage and are at an elevated risk of disease. This course will survey the primary research literature concerning fundamental DNA damage repair pathways, including Base Excision Repair, Mismatch Repair, Nucleotide Excision Repair, and Direct Repair. We will explore the major sources of both nuclear and mitochondrial DNA damage and how mutations that cause imbalances in repair proteins can lead to diseases, including breast, colon and brain cancers; neurological disorders like ataxia telangiectasia and Alpers' disease; and premature aging disorders like Werner's syndrome and xeroderma pigmentosum. We will discuss how an understanding of DNA repair pathways can be utilized in the prevention and management of these diseases. We will consider how different model systems (including yeast, mice, and human cells) are studied in the laboratory to answer fundamental questions concerning DNA damage and genomic instability. We will learn how to critically evaluate the primary scientific literature, with an emphasis on experimental design and the presentation and

interpretation of results. Students will have the opportunity to visit a research facility and to attend research seminars, including the DNA Repair and Mutagenesis seminar series, and in this way meet local scientists in the DNA repair field.

Spring 2014

7.341 Designer Immunity: Lessons in Engineering the Immune System
Instructors: Gregory Szeto (gszeto@mit.edu, 617-253-0656; laboratories of Darrell Irvine and Douglas Lauffenburger)
Talar Tokatlian (talar@mit.edu, 617-253-0656; laboratory of Darrell Irvine)
Spring 2014. Fridays 11 am – 1 pm. (Class time is flexible.) Room 68-150.

The immune system is one of the most complex and powerful of human body systems. It is highly dynamic and flexible, yet strictly regulates homeostasis and protects our bodies from both foreign and self-derived challenges. As basic understanding of immune function is growing, researchers are rapidly designing clever and diverse strategies to manipulate immunology to improve human health. In this course, we will explore important advances rooted in engineering principles to harness the power of the immune system, focusing on how engineering has fueled or inspired research concerning (1) vaccines, (2) immunotherapies, and (3) systems immunology. First we will discuss how engineering can improve the efficacy and efficiency of both delivery of vaccines to immune organs and vaccine-induced immunity. Next we will discuss engineered therapies to manipulate immunology in diseases such as cancer. Then we will focus on systems-based tools, including multivariate profiling and regulatory network analyses that have been developed to predict cell or patient immune responses to vaccines, therapies, and diseases. Many approaches to vaccine design and immunomodulation will be discussed, including therapeutics and prophylactics for influenza, hepatitis B, HIV/AIDS, malaria, cancer, and autoimmunity. Specific examples will include biomaterials as vaccine carriers that have been inspired by the natural biology of microbes and cell lines that have been engineered to use HIV antibodies as calcium signaling receptors to screen candidate HIV vaccines. Engineered therapies and immune system modeling are improving our understanding of immunology as well as our ability to manipulate immunological mechanisms for therapeutic purposes. A broad range of disciplines will be discussed, encompassing the fields of materials science and chemical, biomedical, electrical, and systems engineering. Each session will be driven by student-led discussions of important research articles. Emphasis will be placed on understanding the concepts, experimental techniques and experimental design utilized. Students should then be able to translate their reading of the primary research literature to the laboratory as well as to other real-world applications. We will visit an academic research laboratory or small biotechnology company currently engaged in immunoengineering.

7.342 Personal Genomics and Medicine: What's in Your Genome?
Instructor: Zara Herskovits (aherskov@mit.edu; 3-4140; laboratory of Dr. Leonard Guarente)

Spring, 2014. Thursdays, 11 am – 1 pm. (Class time is flexible). Room 68-150.

Human genome sequencing has revolutionized our understanding of disease susceptibility, drug metabolism and human ancestry. This course will explore how these advances have been made possible by revolutionary new sequencing methodologies that have decreased costs and increased throughput of genome analysis, making it possible to examine genetic correlates for a variety of biological processes and disorders. Each student will have the opportunity either to have the sequence of his/her own DNA determined or to explore publically available genome reference samples to understand what can be learned from examining genetic markers that can correlate with disease risk, carrier status and medication response. We will discuss how an individual's risk of developing a disease can be assessed based on small genetic changes in nucleotide sequence as well as on larger structural variations that affect entire regions of a chromosome. We will also discuss how maternal ancestry, paternal lineage, and human populations can be analyzed by examining chromosomal or mitochondrial DNA. We will read papers from the scientific literature to understand how genetic analysis is influencing treatment for patients who have cancers with specific mutations that can be targeted with tyrosine kinase inhibitors, such as individuals with chronic myelogenous leukemia who have the BCR-ABL fusion protein or patients with non-small cell lung cancer who have an EML4-ALK gene fusion. Genomic analysis has also spurred the development of new drugs that might be helpful for patients in the general population, such as PCSK9 inhibitors for patients with hypercholesterolemia, an approach that was driven by the observation that people with a mutation in this gene have abnormally low LDL cholesterol. We will also debate social, legal and ethical aspects of genetic testing. The course will combine discussions of primary scientific research papers with hands-on data analysis and small group presentations. We will take a field trip to the Harvard Medical School Center for Personalized Genetic Medicine and Medical Genetics at the Brigham and Women's Hospital to learn how genomic sequencing informs clinical decision making.

7.343 Biological Bases of Learning and Memory

Instructors: Jai Subramanian (jai_sub@mit.edu, 46-3225; laboratory of Elly Nedivi) and Lauren Makuch (makuch@mit.edu, 46-3225; laboratory of Elly Nedivi)

Spring 2014. Thursdays, 3 pm – 5 pm. (Class time is flexible.) Room 68-150.

The brain allows animals to have an incredible capacity to acquire information about the world and to encode, store, and later retrieve that knowledge. What are the biological bases of learning and memory? How does the brain come to learn whether a stimulus is annoying, rewarding or neutral, and how does remembering how to ride a bicycle differ from remembering scenes from a movie? In this course, students will explore the concept that learning and memory have a physical basis that can be observed as biochemical, physiological and/or morphological changes to neural tissue. We will critically read and discuss primary research articles to become familiar with several different types of learning and memory and the experiments that have enabled them to be distinguished. Newly learned information is encoded through changes in the strength of

existing connections between neurons, called synapses (the junctions at which neurons communicate with each other), or by formation of new connections and/ or elimination of others. We will discuss the molecular and cellular mechanisms that mediate these changes by exploring concepts such as synapse formation and stabilization, synaptic transmission, synaptic plasticity, neuromodulation and experience-dependent circuit remodeling, among others. With this knowledge, we will discuss how scientists use cutting-edge technologies to introduce false memory in animals or tackle diseases affecting learning and memory, including Alzheimer's disease and mental retardation. We will visit an MIT research laboratory that studies the biological bases of learning and memory or a pharmaceutical company that develops drugs to treat memory disorders. Our goal will be to understand the strategies and techniques biologists use to search for memory traces , the "holy grail" of modern neuroscience.

7.344 Beyond the Code: Emerging Roles of Non-coding RNAs in the Regulation of Gene Expression

Instructors: Johanna Scheuermann (josch@mit.edu, 4-5094; laboratory of Laurie Boyer)
Jessica Hurt (hurt@mit.edu, 3-6726; laboratory of Chris Burge)
Spring 2013. Wednesdays, 3 – 5 pm. (Class time is flexible.) Room 68-150.

The central dogma of biology, "DNA makes RNA makes protein," reflects the function of RNA primarily as a messenger molecule linking the storage of genetic information in DNA to its output as protein. However, recent groundbreaking research has revealed that only a small fraction of all mammalian RNA molecules is actually translated into protein. Seeking the biological roles of this newly appreciated population of non-coding RNAs has quickly emerged as a novel horizon in the RNA field. We now know that many classes of non-coding RNAs, such as microRNAs and long non-coding RNAs, exist and play critical roles as regulatory molecules in the cell. Collectively, these RNA species are involved in every layer of the regulation of gene expression, often employing novel and unexpected molecular strategies. Numerous studies are underway with the goal of deciphering the many functions of non-coding RNAs in controlling differentiation, development, and tissue homeostasis. In this course we will discuss the classes of non-coding RNAs and differences between coding and non-coding transcripts. We will learn about mechanisms by which non-coding RNAs control gene expression, from the level of transcription and chromatin to the regulation of later steps in mRNA biogenesis, including transcription, splicing, polyadenylation and decay. For example, we will learn how microRNAs target specific mRNAs to inhibit protein synthesis and how incorrect expression of these RNAs can have dramatic consequences on cell differentiation and proliferation. We will also discuss how misregulation of non-coding RNAs has been linked to diseases such as cancer and Alzheimer's disease and learn about exciting new therapeutic strategies involving non-coding RNAs, including for the treatment of muscular dystrophy. We are planning a field trip to an RNA laboratory with publications we will have studied in class, so that students will have an opportunity to discuss science directly with the authors and see in real life how the experiments were done. Classes will be based on interactive discussions of the primary research literature and will highlight open questions in the field, aspects of experimental design and data interpretation as well

as the benefits and pitfalls of using different techniques to study non-coding RNAs. Students also will learn about current methodological and conceptual challenges in the RNA field.

7.345 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 2014. Wednesdays, 11 - 1 pm. (Class time is flexible.) Room 68-150.

Genomic DNA is constantly under attack by a wide variety of DNA-damaging agents. Although cells possess multiple DNA repair mechanisms, DNA lesions can escape repair. As a consequence, DNA synthesis can be blocked and single-stranded DNA gaps can be generated. Translesion DNA synthesis (TLS) is a mechanism that helps cells tolerate unrepaired DNA lesions and is carried out 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 from being triggered by catalyzing accurate replication bypass of specific DNA lesions and performing DNA repair synthesis. For example, polymerase h (pol h) accurately bypasses thymine dimers, the major ultraviolet UV 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 resistance to chemotherapy by introducing mutations in crucial genes during error-prone TLS or performing TLS past DNA lesions induced by chemotherapeutic agents. In this case, pol 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 discuss the basics of DNA damage repair and tolerance pathways. We will then turn to the TLS pathway and review the functions of each TLS polymerase and how defects in and/or dysregulation of the functions of TLS polymerases can promote tumorigenesis and chemoresistance. Additionally, we will learn about emerging cancer therapies that target TLS pathways and will explore what other therapies targeting this pathway might be designed to improve current cancer therapeutic strategies. We will focus on the primary research literature, so students will learn how to read and critique research papers. Additionally, we will visit a pharmaceutical company laboratory that is developing anti-cancer drugs.

7.346 The Battle Within - How the Innate Immune System Fights Infection

Instructor: Ana Camejo (acamejo@mit.edu, 5-4031; laboratory of Jeroen Saeij)
Spring 2014. Wednesdays, 1 pm – 3 pm. (Class day and time are flexible.) Room 68-150.

It is one of nature's fiercest battles, in many cases a matter of life and death. Humans are exposed to millions of potential pathogens daily, through contact, ingestion, and

inhalation. Infectious diseases have the potential to decimate millions of people and can emerge naturally as outbreaks or pandemics, or deliberately through bioterrorism. The innate immune system comprises cells and mechanisms that defend the host from infection in a non-specific manner, without conferring protective long-lasting immunity to the host. Innate immune responses depend on a group of proteins and phagocytic cells that recognize conserved features of pathogens and become quickly activated to help destroy invaders. Innate immune responses have been found among both vertebrate and invertebrate animals, as well as in plants. In this course students will learn how to design and critique experiments through the discussion of primary research articles that explore the molecular basis of innate immunity. We will include studies that use vertebrate, invertebrate and plant models. We will discuss a variety of investigative approaches at the forefront of scientific discovery, including genetics, biochemistry, cell biology, and genomics/proteomics. Together, we will understand why the inflammasome is setting our cells on fire and unravel Nobel Prize winning topics, such as Toll-like receptors, the complement system and phagocytosis.

7.347 Epigenetic Regulation of Stem Cells

Instructors: Eric Williams (eow1@mit.edu, 607-351 2831; laboratory of Leonard Guarente)

Joe Wamstad (jwamstad@mit.edu, 617-324-5094; laboratory of Laurie Boyer)

Spring 2014. Thursdays, 1 pm - 3 pm. (Class time is flexible.) Room 68-150.

During development a single totipotent cell gives rise to the vast array of cell types present in the adult human body, yet each cell has essentially the same DNA sequence. As cells differentiate, distinct sets of genes must be coordinately activated and repressed, ultimately leading to a cell-type specific pattern of gene expression and a particular cell fate. In eukaryotic organisms, DNA is packaged in a complex protein super structure known as chromatin. Modification and reorganization of chromatin plays a critical role in coordinating the cell-type specific gene expression programs that are required as a cell transitions from a pluripotent stem cell to a fully differentiated cell type. Epigenetics refers to such heritable changes that occur in chromatin without altering the primary DNA sequence. The ability to study the epigenome (the chromatin-associated proteins and RNAs that organize and coordinate access to DNA) on a grand scale has only recently become feasible with the advent of methods for genome-wide analyses and high-throughput sequencing technologies. For example, we are now able to map essentially any epigenetic modification that occurs to either the DNA itself and or to the chromatin protein scaffold around which the DNA is organized. We can even decipher the 3-dimensional structure of chromatin within the nucleus during different epigenetic states. These advances have led to an explosion of data and a comprehensive picture of the epigenome and the factors that regulate it. In this class we will discuss the various mechanisms of epigenetic regulation, including DNA methylation and post-translational modification of histones, and the roles of chromatin-assembly modifying complexes, non-coding RNAs and nuclear organization. We will read papers from the primary research literature and discuss both the scientific discoveries and the new technologies that have made these discoveries possible. This class will focus on the role of epigenetic

regulation with respect to developmental fate and also consider the fact that the epigenetic mechanisms discussed have broad implications, including how seemingly normal cells can be transformed into cancerous cells.