Advanced Undergraduate Seminars
2016-2017

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Spring 2017

7.341 Peptides as Biological Signaling Molecules and Novel Drugs
Instructor: Mohammed Shabab (shabab@mit.edu, 617-253-3745, laboratory of Graham Walker)
Spring 2017. Wednesdays, 11 am - 1pm. (Class day and time are flexible.) Room 68-150.

All living cells possess the machinery for peptide synthesis, secretion, and posttranslational modifications, which together generate enormous structural and functional peptide diversity. Peptides are broadly used as signal molecules for intercellular communication in 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). In plants, peptide signals such as CLAVATA3 play important roles in development. Peptides are also used as components of 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 specific peptide receptors or interacting proteins for proper function? In this course, we will learn about the molecular bases of peptide signaling. In addition, peptides are promising novel therapeutic agents. For example, antimicrobial peptides (AMPs) have broad spectrum antimicrobial activity against bacteria, viruses, and fungi and are found among all classes of life. The ability of these natural molecules to kill multidrug-resistant microorganisms has gained 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 multidrug-resistant microorganisms are 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 peptides promising future drugs. In this class, we will discuss AMPs, their biological functions, mechanisms of action, and applicability as therapeutic agents. Students will learn about various human defense peptides, such as defensins, 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 Cubist Pharmaceuticals, a pharmaceutical company based in Lexington, MA, which is developing peptides as drugs for various pathological conditions, such as complicated urinary tract infections.

7.343 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)
Spring 2017. Wednesdays, 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 mechanisms has long been appreciated. Mario Capecchi, Martin Evans, and Oliver Smithies made ground-breaking discoveries using mouse embryonic stem cells for gene targeting in mammals. Their efforts made it possible to modify the DNA of specific genes within 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 aspects of those disorders in a cell-culture system. Scientists can now cause such patient-specific stem cells to differentiate into cell types affected by the disease, allowing the study of the diseased cells and an understanding of the mechanisms underlying disease progression. Such 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, we will discuss specific disease model systems and their benefits/limitations for understanding the disease and facilitating the development of treatments for 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.

7.344 You Are More Than the Sum of Your Genes: Epigenetics in Health and Disease
Instructor: Ishara Azmi (ifazmi@mit.edu, 8-7352; laboratory of Steve Bell)
Spring 2017. Thursdays, 11 am – 1 pm. (Class day and time are flexible.) Room 68-150.

Hereditary information is primarily contained within the DNA sequence of cells. Such information has to be faithfully replicated in each cell cycle and transferred to daughter cells to maintain genomic stability, cellular viability and the continuity of life. The field of study of such hereditary information is known as genetics. Epigenetics, or "beyond genetics," encompasses processes that mediate inheritance of information not contained in the DNA sequence. In eukaryotic cells DNA is packaged into a condensed form known as chromatin, which is primarily composed of nucleosomes, each of which consists of about 147 base pairs of DNA wrapped around an octamer of histone proteins. The structure of heterochromatin (regions of compact chromatin that are suppressed in gene expression), histone modification (by phosphorylation, methylation or other processes) and DNA modification (by methylation) carry important epigenetic information from one generation to the next. Epigenetic information can be propagated to the next generation to maintain a functional state, such as whether specific genes are or are not expressed. Such epigenetic gene regulation is important during various stages of development to facilitate cellular differentiation and maintain genomic stability. In this class we will discuss the history of epigenetics, including classical epigenetic phenomena, such as position effect variegation (which results when genes are juxtaposed to heterochromatin, thereby decreasing their expression), polycomb silencing (which involves a group of protein complexes that repress gene activity through regulating chromatin state), dosage compensation (which enhances the transcription of most genes on the only X chromosome in males to match the level in XX females) and mechanisms of epigenetic memory transfer from one generation to another (DNA and histone modifications, heterochromatin formation). We also will discuss mechanisms of epigenetic inheritance during DNA replication and examples of how defects in epigenetic inheritance mechanisms contribute to human diseases. We will consider the experimental designs and techniques that have been employed to study epigenetics at the cellular and molecular levels. Finally, we will learn about cutting-edge research in the field of epigenetics, such as stem cell reprograming and epigenetic regulation by non-coding RNAs (which are transcribed but not translated into protein). Stem cell reprograming, which involves the generation of pluripotent stem cells from mature adult cells, is based on modifying the epigenetic control of gene expression. This technology has the potential to treat and cure a broad variety of human diseases. The major goal of this course is to help students learn to read, comprehend and critique the primary research literature. Students will visit the laboratory of Professor Mary Gehring at the Whitehead Institute. The Gehring laboratory studies epigenetic mechanisms in *Arabidopsis thaliana*, a popular model organism in plant biology. Students will visit the research facility and

observe experimental approaches used to analyze how epigenetic mechanisms modulate plant growth and development.

7.345 Let's Talk About Sex (Chromosomes) and Human Genetics

Instructors: Adrianna San Roman (sanroman@wi.mit.edu, 617-258-5164, laboratory of David Page)
Maria Mikedis (mikedis@wi.mit.edu, 617-258-5164, laboratory of David Page)
Spring 2017. Thursdays, 1 pm - 3 pm. (Class day and time are flexible.) Room 68-150.

The many differences between males and females of mammalian species are driven by a simple disparity in sex chromosome content: males have one X and one Y chromosome, while females have two X chromosomes. Although this difference is widely appreciated, scientists are still learning how these sex chromosomes lead to distinctions between males and females at the cellular and organismic levels. As the only unequal pair of human chromosomes, X and Y have unique genetic properties that influence chromosome segregation, regulation of gene expression, and disease inheritance. During this course, we will take a multidisciplinary approach to delve into the many fascinating aspects of sex chromosome biology. First, we will discuss how the presence or absence of the Y chromosome in mammals determines whether testes or ovaries develop. We will address disorders of sexual development in which the sex chromosomes do not match the physical appearance of the genitals. We will also investigate mechanisms of sex determination in non-mammalian organisms, such as flies, worms, birds, bees, and turtles, which have diverse means of generating phenotypic males or females. We will then read about reconstructing the evolution of the sex chromosomes, which will provide context for understanding current questions in sex chromosome biology. Concurrently, we will learn about the distinctive methods that were used to sequence the sex chromosomes as part of the Human Genome Project. Students will visit the laboratory of MIT Professor Dr. David Page to learn about DNA sequencing and other techniques used today to interrogate current questions concerning sex chromosome biology. Several unique properties of the sex chromosomes will be addressed, including inheritance of the Y chromosome and its relevance for reconstructing familial ancestry and understanding genetic predisposition to disease; the high proportion of repetitive DNA sequences in the Y chromosome that make it particularly susceptible to rearrangements that can lead to infertility; and the process of X-inactivation, which equalizes X chromosome gene expression between males and females and is key for understanding sex-biased manifestations of simple genetic diseases. Next, we will explore human genetic conditions related to abnormal numbers of whole sex chromosomes, such as Turner and Klinefelter syndrome. Finally, we will evaluate emerging evidence that sex chromosomes contribute to sex-specific molecular differences that might influence the pathogenesis of complex sex-biased diseases, such as multiple sclerosis, which is more prevalent in females, and autism, which is more prevalent in males. This course will introduce students to reading and critically evaluating the primary literature that has shaped key aspects of understanding sex chromosome biology**.**

7.346 Bacteria Fight Back – How Bacteria Evade Treatment and Novel Strategies to Outwit Them

Instructors: Julie Silverman (silverjm@mit.edu, 617-253-1834, laboratory of Barbara Imperiali)
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Spring 2017. Thursdays, 3 pm - 5 pm. (Class day and time are flexible.) Room 68-150.

Bacteria and fungi have been producing antibiotics, small molecules that can kill or prevent growth of competing bacteria, since long before humans walked the earth. The discovery of antibiotics and the realization that they could cure bacterial infections radically changed modern medicine. The use of these molecules in the clinic has saved countless lives by eradicating infections that were previously impossible to treat, including syphilis, strep throat and tuberculosis. Although antibiotics were once referred to as the "wonder drugs" of modern medicine, an alarming number of drug-resistant bacteria have emerged since the beginning of the 20th century, compromising the effectiveness of these critical clinical tools. Antibiotic resistance has spread rapidly, leading to the emergence of multi-drug resistant bacteria and threatening the start of a post-antibiotic era. This phenomenon is in large part because bacteria can evolve rapidly to withstand antibiotics, and many species can transfer genes to one another. Research into antibiotic resistance has uncovered many unique mechanisms by which bacteria protect themselves from these threats to their survival, and has also uncovered many interesting aspects of bacterial physiology.

Understanding how bacteria evolve to resist antibiotics will be fundamental for the future of medicine. During this course, we will discuss many aspects of antibiotics, including examples of how particular antibiotics were discovered, specific mechanisms of bacterial resistance, and how antibiotic resistance spreads among bacteria in the environment. For example, we will learn how penicillin was discovered, and then about the resistance mechanisms that arose following its widespread use. We will also discuss antibiotic-resistant bacteria more generally and delve into the molecular mechanisms underlying resistance and the spread of such resistance mechanisms, including point mutations, efflux pumps, and horizontal gene transfer. In addition, we will introduce students to fascinating bacterial behaviors, such as biofilm growth and dormancy, which allow bacteria to become temporarily tolerant of antibiotic treatment even in the absence of classical mutational changes that confer antibiotic resistance. The course will conclude with an examination of today's state concerning antibiotics and antibiotic resistance through a discussion of new pioneering work to treat infections with engineered antimicrobial peptides, bacteriophage therapies and microbiome replacement therapies such as fecal transplants. We will focus on the primary research literature, and we will learn practical laboratory techniques, experimental design and how to interpret data and critique the conclusions offered by authors. Students will have the opportunity to visit a local biotech company to learn about novel approaches to treating bacterial infections that go beyond the traditional small molecule antibiotic.