Advanced Undergraduate Seminars
2017-2018

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Spring 2018

7.341 The Microbiome and Drug Delivery: Cross-species Communication in Health and Disease

Instructors: Miguel Jimenez (jmiguelj@mit.edu, 949-285-0318, laboratory of Robert Langer)
Ali Beyzavi (beyzavi@mit.edu, 617-963-9437, laboratory of Robert Langer)
Spring 2018. Wednesdays, 11 am – 1 pm. (Class day and time are flexible.) Room 68-150.

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

7.343 Bringing SeXY Back: Sex Chromosome Genetics and Genomics in Development and Disease

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 2018. Wednesdays, 3 - 5 pm. (Class day and time are flexible and will be finalized after the first class.) 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 and no Y chromosomes. Although this difference is widely appreciated, scientists are still learning how the sex chromosomes lead to distinctions between males and females at the cellular and organismic levels. Because X and Y differ in gene content and are therefore the only pair of human chromosomes that are not true homologs, 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 the biology of sex and sex chromosomes. First, we will discuss the genetics of sex determination of various organisms as well as sex-chromosome-driven disorders of sexual development. We will consider how new findings are revising thoughts about the evolution of the sex chromosomes and how these evolutionary considerations are providing context for understanding current questions in sex chromosome biology. Several unique properties of the sex chromosomes will be addressed, including the relevance of the Y chromosome in reconstructing familial ancestry and the role of the sex chromosomes in genetic predisposition to disease and infertility. We will explore human genetic conditions related to fewer or extra sex chromosomes, such as Turner (only one X and no Y) and Klinefelter (two Xs and one Y) syndromes. 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. We will visit the laboratory of MIT Professor Dr. David Page to observe molecular methods used in studies of sex chromosome biology, including preparing a genome to be sequenced via cloning, next-generation DNA sequencing, and computational genome assembly. This course will teach students to read and critically evaluate the primary research literature that has shaped today's understanding of sex chromosome biology.

7.344 ATP-powered Motors: The Engines of Life
Instructors: Theodore Moore (tcmoore@mit.edu, 734-255-0295, laboratory of Tania Baker)
Hema Chandra Kotamarthi (hchandra@mit.edu, 857-218-8714, laboratory of Tania Baker)
Spring 2018. Thursdays 1-3 pm. (Class day and time are flexible.) Room 68-150.

Life requires movement, be it walking to the grocery store or pulling apart chromosomes. On the cellular level, a host of nanomotors perform work to accomplish essential movements. These nanomotors are assemblies of protein molecules that are often powered by adenosine triphosphate (ATP), sometimes called the fuel of life. ATP-powered nanomotors convert the chemical energy of ATP into mechanical energy, which is used to generate force. This process is analogous to how a car's engine converts the chemical energy of gasoline into force to power the wheels. ATP motors apply their force to a wide variety of cellular activities, such as motility,

cargo transport, DNA packaging, and many others. Defects in ATP motors can lead to diseases, including peripheral neuropathy (a very common disorder involving weakness, numbness and pain) and sideroblastic anemia (a multi-organ disorder caused by a failure of hemoglobin to incorporate iron). Disregulation of certain ATP motors has also been implicated in cancer metastasis. ATP motors come in all sizes and shapes, from kinesin (molecular weight ~400 kDa), which literally "walks" along larger proteins, to the proteasome complex (molecular weight ~2,800 kDa), which degrades cellular proteins. Given the diversity of ATP motors, how can one reaction, the hydrolysis of ATP, drive all these functions? How do these different nanomotors translate chemical energy into work? How do we measure the movements and forces generated by these tiny motors? In this course we will address such questions through reading, discussion and critical evaluation of the primary research literature. We will draw on both classical and modern sources to help understand how researchers have studied the workings of these molecular nanomotors. Students will learn how our knowledge and experimental approaches towards ATP motors have changed over time. Much of the course will be dedicated to discussing recent advances in structural and biophysical techniques, such as cryo-EM (which uses very low temperatures to image large, multiprotein complexes) and single-molecule force spectroscopy (which applies and measures forces using lasers, magnetic fields, and nanoscale probes). These techniques are revolutionizing the structural and mechanistic studies of many macromolecular complexes, including ATP-powered motors. Students will observe single-molecule optical tweezers experiments in the laboratory of Dr. Tania Baker, who explores the mechanisms of proteases such as ClpXP and ClpAP, ATP-powered nanomotors that control protein unfolding and degradation. By the end of the course, students should be able to comprehend and critically assess experimental designs and published claims in the field of ATP motors and in biomedicine more generally.

7.345 Peptides as Biological Signaling Molecules and Novel Drugs

Instructors: Mohammed Shabab (shabab@mit.edu, 617-253-3745, laboratory of Graham Walker)
Cesar de la Fuente (cfuente@mit.edu, 617-324-4227, laboratory of Tim Lu)

Spring 2018. Wednesdays, 11 am – 1 pm. (Class day and time are flexible.) Room 68-150.

All living cells possess a machinery for peptide synthesis, secretion, and posttranslational modifications. An enormous structural and functional diversity of peptides is generated by this cellular machinery. Peptides are broadly used as signal molecules for intercellular communication in prokaryotes, plants, fungi, and animals. Peptide signals in animals include a myriad 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 play important roles in development. Peptides are also used by many organisms as key components of their host defense systems. What determines the functional specificity of each peptide? How do these tiny polymers of amino acids survive hostile protein-digesting enzymes? How are peptides able to communicate with their specific peptide receptors or other interacting proteins for proper function? In this course, we will learn about the molecular bases

of peptide signaling. In addition, peptides exhibit broad-spectrum antimicrobial function and represent promising alternatives to conventional antibiotics for the treatment of infectious diseases. For example, antimicrobial peptides (AMPs), which are found among all classes of life, are low molecular weight proteins with broad spectrum antimicrobial activity against bacteria, viruses, and fungi. These natural molecules are capable of killing multidrug-resistant microorganisms that are otherwise untreatable with available antibiotic therapy. One of the most notorious examples of multidrug-resistance involves MRSA, deadly strains of methicillin-resistant *Staphylococcus aureus*. Infections with these pathogenic bacteria are untreatable with known antibiotics, such as gentamicin, streptomycin and kanamycin. Some antimicrobial peptides can kill methicillin-resistant S. aureus strains, making such molecules promising next-generation 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 the quantification of small molecules such as peptides. We will focus on the primary research literature, and students will learn how to read and critique research papers. Additionally, during this course we will visit a pharmaceutical company in the Boston area.