Advanced Undergraduate Seminars
2017-2018

Fall 2017

7.341 Metabolism in Human Disease

Instructors: Laura Danai (ldanai@mit.edu, 5-4523; laboratory of Matthew Vander Heiden)
Alexander Muir (amuir@mit.edu, 5-4523; laboratory of Matthew Vander Heiden)
Fall 2017. Thursdays, 11 am- 1 pm. (Day and class time are flexible; TBD at first class.) Room 68-150.

Cancer is the second leading cause of death in the United States and has been the focus of sustained public health attention since the 1970s with the passage of the National Cancer Act. This war on cancer has led to substantial progress in treating and preventing many cancers. However, the alarming increase in the prevalence of obesity and diabetes, important risk factors for many cancers, is erasing gains made in the war on cancer. As diabetes and cancer become more prevalent, it is of increasing importance to understand the connections between these disorders. Underlying both diseases are dramatic changes in cellular metabolism, the basic energy and mass-producing biochemical reactions of the cell. In this course, we will explore how altered metabolism drives cancer and diabetes and ask: How do our bodies regulate sugar levels? Why do tumors consume more sugar than normal cells? How do certain diets promote diabetes and cancer growth? How does a drug used to treat diabetes also decrease cancer incidence and death? As we explore these topics in biology and their medical implications students will learn (1) how to read, discuss, and critically evaluate scientific findings in the primary research literature, (2) how scientists experimentally approach fundamental issues in biology and medicine, (3) how recent findings have challenged the traditional "textbook" understanding of metabolism and given us new insight into cancer and diabetes, and (4) how a local pharmaceutical company is developing therapeutics to target cancer metabolism in an effort to revolutionize cancer therapy.

7.342 How To Build An Animal: Cell Fate and Identity in Development and Disease

Instructors: Laura Blanton (lblanton@wi.mit.edu, 617-258-5174; laboratory of David Page)
Andrew Knutson (aknutson@wi.mit.edu, 617-258-5174; laboratory of David Page)
Fall 2017. Tuesday, 3 pm - 5 pm. Room 68-150.

Multicellular organisms develop from single cells that form as a result of fusion between two haploid gametes, e.g., sperm and egg. The fertilized egg, known as a zygote, undergoes a series of dynamic developmental events to give rise to a multitude of cell types, such as neuronal cells in the brain and central nervous system and hematopoietic cells that generate the immune system. Understanding how these different cell types, each with their own unique functions, are generated from the totipotent zygote is a major goal of research in the fields of developmental biology and biomedicine. Because most cells within a given organism contain the same genetic information regardless of differentiated state, cell identity is manifested

through a number of molecular mechanisms that influence cellular behavior and function without altering DNA sequence. In this course, we will explore how animals determine and maintain cell fate and discuss changes to DNA structure and packaging, special proteins (known as “master regulators”) with the ability to alter cell fate via transcription, cell-cell signaling, and RNA localization. We will examine how researchers have defined cell identity and potency and analyze critical papers describing the discovery and characterization of stem cells, which are undifferentiated cells able to give rise to multiple cell types. Additionally, we will examine the development and maintenance of numerous specialized cell types considering, for example, evolutionarily conserved developmental pathways that lead to a germ cell (sperm or egg) identity as opposed to a somatic (non-germ) cell identity in a variety of animal species. We will discuss crucial somatic developmental pathways, including the restriction of cell fate in differentiating hematopoietic lineages. We will conclude by examining how failure to maintain proper cell fate and identity can lead to disease and consider disorders of sexual development as well as a number of cancers.

7.343 Host Pathogen Interactions: Biology and Disease of Parasitic Manipulations

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

Diego Huet (dhuet@wi.mit.edu, 617-324-5869, laboratory of Sebastian Lourido)

Fall 2017. Fridays, 4 pm - 6 pm. (Class day and time are flexible.) Room 68-150.

Parasites have evolved multiple strategies to subvert their hosts in order to reproduce and spread. These pathogens scavenge nutrients directly from host cells, evade the host immune system and even modify host behavior to increase their transmission. This course will explore the strategies used by a ubiquitous and harmful class of parasites to hijack the biology of their host cells. This class includes pathogens such as *Plasmodium* and *Toxoplasma*, responsible for some of the deadliest and most prevalent diseases on the planet. Malaria is caused by several *Plasmodium* species and causes more than half a million deaths a year, mostly of children under five. After being transmitted through a mosquito bite, *Plasmodium* invades the liver and red blood cells. One of the most important manifestations of malaria is the modification of red blood cells by the parasite, causing them to stick to the walls of small blood vessels. Vessel blockage in the brain causes cerebral malaria, the most fatal form of the disease. As a pathogen of humans for the past 100,000 years, *Plasmodium* has evolved elegant strategies to survive and ensure its transmission, for example by hijacking the human immune system. It has also been suggested that *Plasmodium* alters the behavior of infected mosquitos by making them more likely to seek hosts and to feed more often, thereby increasing the transmission of the parasite. Another parasite, *Toxoplasma gondii*, might be the world’s most successful pathogen, infecting up to half the human population. Although its sexual cycle takes place only within cats, *Toxoplasma* is able to survive within almost all warm-blooded animals. In humans, *Toxoplasma gondii* causes a chronic and asymptomatic infection in immuno-competent subjects. However, in immuno-compromised patients, *Toxoplasma* can cause fatal brain inflammation. *Toxoplasma* infection of otherwise healthy pregnant women can cause miscarriage, and *Toxoplasma* variants are a leading cause of eye disease in otherwise healthy

people in South America. Intriguingly, chronic *Toxoplasma* infection has been linked to host behavioral alterations; for example, infected mice lose their fear of cats, increasing their chance of being eaten and so completing the parasite's lifecycle. In humans, *Toxoplasma* infection has been associated with risk-taking behavior and might be involved in schizophrenia. By exploring how these pathogens invade a host cell and replicate while evading the host's immune system, students will gain a broad understanding of basic cell biology, biochemistry and immunology, as well as gain familiarity with techniques commonly used in cell biology. A major goal of the course will be to teach students to critically analyze the primary research literature. Students will be challenged to think creatively and flexibly to understand, critique, interpret, and design scientific experiments in the field of host-pathogen interactions. This course will include a field trip to an academic laboratory focused on host-pathogen interactions, where students will learn about the use of several cutting-edge techniques for the study of the biology of *Toxoplasma* and the impact that these tools are having on the fast-moving field of molecular parasitology.

7.344 Glycans: The Most Important Class of Biomolecule You've Never Heard Of

Instructors: Nathaniel Schocker (schocker@mit.edu, 617-253-1834, laboratory of Barbara Imperiali)

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Fall 2017. Wednesdays, 3-5pm. (Class day and time are flexible.) Room 68-150.

A parasite escapes detection by its host by using camouflage and decoys. A mouse gene goes from silenced to expressed simply by the addition of eight carbon atoms. A breast cell becomes cancerous and alters its membrane to look like a white blood cell instead, a change important in metastasis. What do these seemingly distinct processes have in common? All are made possible by glycans, complex essential sugars attached to proteins and other biomolecules. The U.S. National Institutes of Health named glycans the most important biomolecule class of this decade, and the global funding for glycan research is expected to double by 2021. Completely distinct from metabolic sugars, glycans are generated and destroyed by hundreds of enzymes and are vital to nearly every biological process. So why might you not have heard more about glycans? The complexity of glycan architecture has made studying these biomolecules particularly challenging. In this course, we will discuss how biologists and chemists alike craft experiments to uncover the many ways in which glycans impact human biology and disease and how these insights are being leveraged to create therapeutics as well as tools to identify and manipulate glycans. By reading the primary literature, you will learn the fundamentals of the field of glycobiology – what makes a glycan, how glycans differ, how various organisms utilize glycans as an aspect of normal biology and how glycan biology is important in human disease. Through reading and class discussion, you will learn the art of experimental design. By the end of the course, you should be able to generalize your insights to many other areas of life science research. More specifically, we will consider questions such as: Why do eukaryotes and prokaryotes use different glycans for seemingly similar functions? How are glycans and glycoconjugates synthesized in humans, and how can such syntheses be done efficiently in the laboratory? How does this special chemical class exemplify the interface between chemistry

and biology? How do glycans reflect and enable the progression of cancers? What kinds of tools do researchers use to study such small, difficult-to-handle molecules, and what more need to be invented? What kinds of inherited or acquired diseases are caused by glycan defects, and how can such disorders be treated? Might animal-to-human organ transplantation be aided by modifying foreign glycans to look more like human ones? In this course you will learn answers to all of these questions.

Spring 2017

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.

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

Instructor: Michele LeRoux (leroux_m@mit.edu , 617-253-3677, laboratory of Michael Laub)
Spring 2018. Wednesdays, 1 -3 pm. (Class time is flexible.) Room 68-150.

Bacteria and fungi have been producing antibiotics, small molecules that can kill or prevent growth of competing bacteria, for billions of years – 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 antibiotics in the clinic has saved countless lives by allowing us to treat common infections that were previously a death sentence, including syphilis, strep throat and cholera. 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, which have been using these molecules to fight one another for eons, are already adept at evolving the ability to withstand antibiotics. Furthermore, many species can transfer antibiotic resistance genes to one another. During this course, we will discuss many aspects of antibiotics, the processes by which bacteria survive antibiotic treatment, and alternative approaches to treating bacterial infections to avoid issues of resistance. We will begin by examining how particular antibiotics were discovered and the specific mechanisms of bacterial resistance that have arisen (e.g. vancomycin and vancomycin-resistance mechanisms). We will examine the spread of antibiotic resistance genes from an ecological and mechanistic perspective to understand how the widespread human use of antibiotics continues to accelerate this process. In addition to antibiotic resistance, treatment of infection is hampered by a plethora of other bacterial tricks, such as biofilm growth and temporary drug tolerance. We will delve into a few of these fascinating mechanisms and learn how they are also contributing to classical resistance. The course will conclude with a discussion of recent attempts to find novel antibiotics as well as alternatives to antibiotics, such as microbiome replacement therapies (e.g. fecal transplants). Each topic will be explored by reading and discussing the primary research literature. To facilitate understanding of this literature, we will discuss a broad range of relevant laboratory techniques, principles of experimental design, the interpretation of data, and critical analysis of the conclusions offered by authors. Students will have the opportunity to visit a local biotech company to learn about cutting-edge approaches to treating bacterial infections.

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

Instructor: 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.