Advanced Undergraduate Seminars
2012-2013

Fall 2012

7.341 Harnessing the Biosphere: Natural Products and Biotechnology

Instructors: Christopher Brigham (cbrigham@mit.edu, 617-253-5106; laboratory of Tony Sinskey)
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Fall 2012. Thursdays 11 am – 1 pm. (Class time is flexible.) Room 68-150.

Biotechnology is a rapidly growing field that offers alternative ways to produce substances that previously were either made by complex chemical syntheses or impossible to produce. What do the organisms of the biosphere, specifically microorganisms, have to offer to biotechnological endeavors? The advantages of using microbes include the use of carbonic waste streams (*e.g.* food and crop waste) or CO_2 for the production of products that are useful to us (biofuels, amino acids, etc.), fewer toxic waste byproducts than in chemical syntheses, and the possibility of producing highly complex molecules economically. Our ever-increasing repertoire of controllable biological functions (encoded by the genes present in an organism) allows for the efficient production of a broad variety of biomolecules. The number of possibilities grows as synthetic biology (the ability to synthesize DNA and design genes at will) progresses in its ability to alter microorganisms and enzymes to make chemical structures that have never existed. In this course we will focus on the production of biomolecules using microbial systems. We will discuss potential growth substrates (such as agricultural waste and CO_2) that can be used and learn about both established and cutting-edge manipulation techniques in the field of synthetic biology. This course will include the production of biofuels, bioplastics, amino acids (*e.g.* lysine), food additives (*e.g.* monosodium glutamate, MSG), specialty chemicals (*e.g.* succinate), and biopharmaceuticals (*e.g.* plasmids for gene therapy). We will learn how microbes have been used for several millennia to produce flavorings and alcoholic beverages (*e.g.* wine and beer) and discuss how biotechnology has been used to enhance the production capabilities of such microbial strains. We also will discuss the production of enzymes that can be purified and used in various applications: have you ever wondered why you can wash your clothes at low temperatures? In addition, we will consider the production of medically relevant substances, such as antibiotics and biocompatible materials (*e.g.* polymers for tissue implants and tissue-engineering scaffolds). We are planning a field trip to a biotech company in the Cambridge area to learn how molecular biology and microbiology research can directly lead to the production of marketable compounds like plastics, medicines, and food additives.

7.342 To Divide or Not To Divide: Control of Cell Cycle and Growth by Extracellular Cues

Instructors: Folkert van Werven (folkert@mit.edu, 3-3045; laboratory of Angelika Amon)
Alexi Goranov (goranov@mit.edu, 3-3045; laboratory of Angelika Amon)

Fall 2012. Wednesdays 11 am - 1 pm. (Class time is flexible.) Room 68-150.

All organisms are composed of cells. These cells, regardless of whether they are in an organ in the human body or a component of a bacterial colony, can sense the chemical composition of the environment, the presence of neighboring cells, and even the types of their neighboring cells. Depending on the identity of a cell and the information it receives from its environment, it can grow (increase in size), proliferate (make more cells), become quiescent (stop growing and dividing), differentiate (make different types of cells), or die. Failure of cells to properly respond to their environmental signals can lead to a loss of fitness and competitive advantage for the organism, inability to regenerate tissue loss, or to a disease, such as cancer or diabetes. How cells achieve the astonishing feat of appropriately sensing and responding to their environment has been a major question in biology. In this course we will read and critically discuss the primary scientific literature with the goal of highlighting the basic principles of cell growth, adaptation, and differentiation. We will cover diverse examples of the responses of cells to environmental stimuli and the mechanisms cells use in such responses. We will discuss how bacteria count their number and differentiate only when a "quorum" is present, how cells respond to starvation by performing specialized cell divisions, how cells control their growth in response to nutrients and hormones, how different cell types from the same organism respond to the same stimulus differently, how loss of proper growth control leads to cancer and a variety of other topics. We will pay special attention to the techniques and approaches that have allowed investigators to address these various issues. Towards the end of the course, we will visit a research lab and observe first-hand some of the techniques and instruments we have learned about from our readings and discussions.

7.343 Network Medicine: Using Systems Biology and Signaling Networks to Create Novel Cancer Therapeutics

Instructor: Mike Lee (mikejlee@mit.edu, 617-452-2443; laboratory of Michael Yaffe)

Fall 2011. Wednesdays, 1 - 3 pm. (Class time is flexible.) Room 68-150.

Complex human diseases—like cancer, diabetes, or autism—involve dysregulation of numerous genes, proteins, and cellular behaviors. Creating effective therapies for these diseases will require a comprehensive understanding of how cells integrate enormous amounts of genomic, proteomic, and environmental information to produce specific cellular functions, and furthermore, how such functions have been perturbed in the disease state. To meet this challenge, many have turned to systems biology, an interdisciplinary field that integrates biology with principles borrowed from mathematics, physics, and engineering to gain a comprehensive understanding of biological complexity. In this course, we will survey the primary systems biology literature, particularly as it pertains to understanding and treating various forms of cancer. We will consider various computational and experimental techniques being used in the field of

systems biology, focusing on how systems principles have helped advance biological understanding. Topics will include: various methods of quantitative high-throughput data acquisition, genomic analysis, signaling network biology, and statistical/computational modeling. We will also discuss the application of the principles of systems biology and network biology to drug development, an emerging discipline called "network medicine." We will take field trips to local systems biology meetings and to Merrimack Pharmaceuticals, a Cambridge area pharmaceutical company that is using systems biology to create new anti-cancer agents.

7.345 Chaperones at the Dance: How Cells Deal With Inappropriate Behavior of Proteins

Instructors: Tejas Kalastavadi (tejas @mit.edu, 2-3927; laboratory of Tania Baker)
Adrian Olivares (olivares @mit.edu, 8-8122; laboratory of Tania Baker)
Fall 2012. Wednesdays, 3 - 5 pm. (Class time is flexible.) Room 68-150.

Every cell performs a remarkable array of wonderfully complicated processes that require the actions of properly folded proteins. However, proteins frequently unfold, misfold or get damaged during the life of a cell, particularly during times of stress. Aberrant protein folding often leads to loss of protein function and unwanted self-association, or aggregation. Such misbehavior contributes to the pathology of several important diseases, including Alzheimer's, Parkinson's and type II diabetes, which have been linked to the accumulation of toxic, misfolded proteins. This course will focus on how cells detect and treat unfolded, misfolded and aggregated proteins. Cells use molecular "chaperones" to help maintain proteins in an unfolded state or to catalyze the proper refolding of misfolded proteins. Cells also remove misfolded proteins through a carefully regulated process of protein degradation. We will review the intracellular machinery required for these processes and how the discovery of this machinery led to a Nobel Prize in Chemistry in 2004. We also will discuss novel therapeutics that target protein quality control pathways. A field trip to a pharmaceutical company will help highlight the development of therapies that target the protein quality control network to combat neurodegenerative diseases and cancer.

7.346 Powerhouse Rules: The Role of Mitochondria in Human Diseases

Instructors: Dan Ferullo (ferullo@mit.edu, 3-3745; laboratory of Graham Walker)
Asha Jacob (aijacob@mit.edu, 3-3745; laboratory of Graham Walker)
Fall 2012. Thursdays, 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 1,500 proteins found in a mitochondrion are nuclear-encoded, 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 remaining encode mitochondrial-specific translational

machinery. A variety of clinical disorders involve molecular defects in mitochondrial function. For example, 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 defects in apoptosis (also known as "programmed cell death") in cancer cells, thereby allowing cells that should die instead to survive and proliferate. In this class, we will learn about the importance of proper normal mitochondrial function in eukaryotic cells. We will also discuss the quality control mechanisms that protect cells from malfunctioning in mitochondria. Lastly, we will learn about how abnormal mitochondrial function and aberrant mitochondrial quality control mechanisms are found in diseases like Parkinson's, cancer, amyotrophic lateral sclerosis (ALS) and mitochondrial DNA depletion syndromes (MDDS).

7.347 Non-coding RNAs: Junk or Critical Regulators in Health and Disease?

Instructors: Nadya Dimitrova (nadyad@mit.edu, 3-0263, laboratory of Tyler Jacks)
Thales Papagiannakopoulos (thalesp@mit.edu, 3-0263, laboratory of Tyler Jacks)

Fall 2012. Thursdays, 3 – 5 pm. (Class time is flexible.) Room 68-150.

For years, the central dogma of biology postulated that RNAs have primarily two functions in cells – mRNAs transmit the information between DNA and proteins, whereas ribosomal and transfer RNAs perform critical tasks in the process of protein biosynthesis. Vast regions of the genome that are transcribed into RNAs but do not encode proteins were considered by many "junk." The recent astonishing discovery that RNAs can regulate the expression of genes independently of protein synthesis has revolutionalized modern biology. The aim of this class is to introduce the diversity of the RNA world, inhabited by microRNAs, lincRNAs, piRNAs, CRISPR RNAs, and many other RNA molecules that do not encode proteins. Over the past decade, these non-coding RNAs have gained a growing recognition for their roles in a wide scope of processes, ranging from embryogenesis and development to cancer and degenerative disorders. We will discuss landmark studies that offer a historical perspective about how meticulous unbiased analyses of basic biological phenomena led to the discovery of non-coding RNAs and elucidated some of their functions. We will also read papers from the latest issues of scientific journals to learn about the most recent developments in this rapidly evolving field as well as discuss the recent explosion of technological advances that allow us to take a snapshot of the RNA population in a cell. Our goal is to glean insights into the functional importance of non-coding RNA molecules and to understand the diverse mechanisms of their action. We will discuss how changes in non-coding RNAs can lead to diseases, such as cancer and artherosclerosis, and how we might explore the therapeutic potential of using non-coding RNAs to treat disease. Throughout the semester, we will assess the evidence that indicates that non-coding RNAs are not merely "junk" but rather critical regulators in health and disease.

Spring 2013

7.340 Unusual Biology: The Science of Emerging Pathogens
Instructors: Ana Camejo (acamejo@mit.edu, 5-4031; laboratory of Jeroen Saeij)
Dan Gold (oro27@mit.edu, 5-4031; laboratory of Jeroen Saeij)
Spring 2012. Thursdays, 1 pm – 3 pm. (Class time is flexible.) Room 68-150.

Infectious diseases represent a serious global public health problem. They have the potential to kill millions of people, whether they emerge naturally as outbreaks or pandemics, or deliberately through bioterrorism. Each day, infectious disease scientists serve on the front lines protecting us from such threats. Emerging pathogens are those that appear in a human population for the first time or are expanding into areas and populations where they have not previously been reported. These organisms have evolved specialized strategies for proliferation and survival in their hosts, and these strategies often involve unique biological processes. Such processes range from atypical cell biology intrinsic to the pathogen to alterations in the behavior of the host caused by the pathogen. 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 disease caused by emerging pathogens. Some examples of diseases caused by emerging pathogens are the Bubonic Plague, Toxoplasmosis, African Sleeping Sickness and Chagas Disease. We will include studies that use a diversity of scientific methods and will discuss a variety of investigative approaches, including genetics, biochemistry, cell biology, and genomics/proteomics. Refreshments will be provided during class. Students will have the opportunity to visit a research facility that practices the techniques and concepts discussed in the class and the option to attend research seminars.

7.341 Fostering and Killing the Messenger: The Post-transcriptional Fate of mRNA
Instructors: Igor Ulitsky (ulitskyi@gmail.com, 8-8346; laboratory of David Bartel)
Schraga Schwartz (schwartz@broadinstitute.org, 857-250-6924; laboratories of Eric Lander and Aviv Regev)
Spring 2013. Fridays, 11 am – 1 pm. (Class time is flexible.) Room 68-150.

The blueprint for making proteins is stored in cells in the form of DNA, but to realize its full and versatile potential, the genome must be transcribed into RNA molecules that are then modified into messenger RNAs (mRNAs) and translated into proteins. This process is subjected to extensive regulation, which is critical to ensure precise expression of the specific repertoire of proteins establishing cell-type-specific cell identities. Some of the most fascinating forms of gene regulation affect RNA following transcription and can have dramatic effects on the identity and the quantity of the protein that is eventually produced. Such regulatory pathways if perturbed can result in human diseases (as many as one-third of hereditary diseases are caused at least in part by pre-mRNA splicing problems) and are being increasingly examined in strategies for therapeutic intervention in diseases such as Duchenne muscular dystrophy and spinal muscular atrophy. In this course we will explore the major steps of control during the life of a protein-coding RNA, and we will discuss the functional consequences of the impairment of each such step. Topics will include RNA splicing, addition of poly(A) tails, export from the nucleus,

localization to specific structures (e.g., synapses), translation, and decay. We will also discuss RNA interference (RNAi), a process in which RNA molecules can direct specific degradation of other RNAs, and will consider the therapeutic potential of RNAi. We will learn about both traditional and cutting-edge approaches for studying the processing events experienced by the mRNAs expressed in a cell (its "transcriptome") from the single-gene to the transcriptome-wide levels, including high-throughput RNA sequencing and associated computational and statistical challenges. Emphasis will be put on critically interpreting experiments in the primary research literature. The course will include a visit to a pharmaceutical company developing RNAi-based therapeutics.

7.342 Dodging the Bullet: Mechanisms of Sensitivity and Resistance to Cancer Therapeutics

Instructors: Ian Cannell (icannell@mit.edu 617-816-3205; laboratory of Michael Yaffe)
Karl Merrick (kmerrick@mit.edu 646-709-3132; laboratory of Michael Yaffe)
Spring 2013. Thursdays 11 am – 1 pm. (Class time is flexible.) Room 68-150.

The goal of personalized cancer medicine is to develop drugs and diagnostic markers that allow patients to be matched to their best therapeutic option. In the clinic today, patients are often treated with both broad-spectrum and so-called "targeted" therapies. Broad-spectrum chemotherapeutics typically work by causing extensive DNA damage that is toxic to cancer cells *and* normal tissues. For example, Cisplatin and related drugs are the standard of care for lung cancer, and their effects are due to the generation of DNA cross-links that are sufficient to trigger the DNA damage response. By contrast, targeted agents seek to specifically kill cancer cells by exploiting a tumor's inherent vulnerabilities, such as those caused by a genetic mutation. For example, Gleevec, an ABL kinase inhibitor, has been successfully used to treat tumors that become "addicted" to mutated, hyperactive ABL kinase activity. Although this approach has yielded remarkable response rates in certain cancer-types, many patients relapse as the result of acquired resistance. Such relapse is true not only for targeted therapies but also for broad-spectrum chemotherapeutics, thus highlighting the need to understand—and overcome—drug resistance mechanisms. In this course, through critical reading of primary research papers, we will discuss the design and implementation of targeted therapy strategies as well as the mechanisms of resistance to these drugs at the molecular, cellular and organismal levels. By discussing these papers students will learn how to interpret, critique and design experiments and to determine what conclusions can and cannot be reached from the given data. We will also discuss the future of personalized cancer medicine in light of what we learn about therapeutic resistance.

7.343 Engineered Microbes: Making the Fuels, Chemicals and Drugs of Tomorrow

Instructor: Jose L. Avalos (javalos@wi.mit.edu, 8-5234; laboratory of Gerry Fink)
Spring 2013. Thursdays, 3 pm – 5 pm. (Class time is flexible.) Room 68-150.

Microbial biotechnology is experiencing an unprecedented boom. Engineered microbes such as bacteria, cyanobacteria, algae, yeasts and molds are being developed for a broad

range of applications, including renewable energy, biomaterial manufacturing, chemical synthesis, and production of drugs and biological agents. Microbes have been engineered to produce advanced biofuels to substitute for gasoline as well as diesel and jet fuel. Such biofuels are being generated not only from glucose but also from cellulose, which substantially reduces competition with food production by utilizing the inedible parts of crops, as well as plants that grow in land unsuitable for agriculture. Biofuels are also being produced with engineered microbes that fix CO_2 using light, hydrogen or electricity, eliminating completely the need for plant-based raw materials. Other microorganisms have been designed to make bioplastics that are biodegradable; spider silk, which is stronger than steel and tougher than Kevlar, DuPont's bulletproof material; and mussel adhesive, which is water resistant, non-toxic and comparable in strength to human-made glues. There are engineered microbes that use renewable sources to make commodity chemicals (raw materials for the chemical industry) traditionally produced from petroleum, and other microorganisms have been engineered to borrow from nature's palettes and bouquets to produce dyes, fragrances and flavors. Microbial engineering is also having an impact on human health. Biological agents such as vitamins, steroids, and vaccines are being produced with engineered microorganisms. Monoclonal antibodies, proteins that can bind and inhibit or activate cellular molecules with high specificity and that are being used to treat many diseases, are now being synthesized in humanized yeast, engineered to have the human machinery for antibody assembly and thus make antibodies that are indistinguishable from those made in human cells. Genetically engineered microorganisms are also being developed to assist in the production of drugs that are difficult to harvest from nature or to synthesize chemically, including drugs to treat cancer, infectious diseases and immune disorders. Microbial engineering is benefiting from many elements of modern biotechnology, including bioinformatics, enzyme engineering, biosensor technologies, directed evolution and global cellular engineering. In this course, we will discuss over snacks research papers from the primary scientific literature concerning these technological developments. We will visit an industrial facility that is applying some of these technologies and attend research seminars by leaders in the field. We will ask critical questions about the engineering strategies that have been used and the potential future directions in this field, in which the possibilities seem limitless.

7.344 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 2013. Wednesdays, 3 pm - 5 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 fully differentiated cell type. Epigenetics refers to such heritable changes that occur in chromatin without altering the primary DNA sequence. The phenomenon of epigenetics and the concept of increasingly restricted developmental potential were first postulated in 1942 by Conrad Waddington. However, the ability to study the epigenome (the chromatin-associated proteins and RNAs in charge of organizing and coordinating access to DNA) on a grand scale has only recently become feasible with the advent of 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 modes of epigenetic regulation, including DNA methylation, post-translational modification of histones, chromatin modifying complexes, non-coding RNAs and nuclear organization. We will 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 concerning how seemingly normal cells can be transformed into cancerous cells.

7.345 Using Simple Organisms to Model Human Diseases
Instructor: Katie Harris (kpharris@mit.edu, 46-3251; laboratory of Troy Littleton)
Spring 2012. Wednesdays, 11 am – 1 pm. (Class time is flexible.) Room 68-150.

How do scientists discover the basic biology underlying human diseases? Simple organisms such as baker's yeast, nematodes, fruit flies, zebrafish, mice and rats have allowed biologists to investigate disease at multiple levels, from molecules to behavior. In this course students will learn strategies of disease modeling by critically reading and discussing primary research articles. We will explore current models of neurodegenerative diseases such as Parkinson's disease, childhood genetic diseases such as Fragile X syndrome, as well as models of deafness and wound healing. Using these examples, we will discuss the pathology of each disease and consider the benefits and drawbacks of a variety of experimental approaches. Some researchers use "environmental" models in which pharmacological agents are used to perturb in an experimental organism the molecules or cells that correspond to those affected in human patients. Alternatively, if a specific gene is known to be linked to a disease, many powerful tools exist to create "genetic" models: researchers can remove, mutate, overexpress or misexpress the gene in an experimental organism to attempt to recreate what happens in the cells of a human patient. Finally, researchers can design genetic screens to identify new genes that might be involved in a particular disease process. We will discuss these approaches as well as the advantages offered by each simple organism. We will visit an MIT research lab that currently studies Huntington's disease using the fruit fly *Drosophila melanogaster*. Our goal will be to understand the strategies biologists

use to build appropriate models of human disease and to appreciate both the power and limitations of using simple organisms to analyze human disease.

7.346 Virus-host Interactions in Infectious Diseases

Instructors: Sumana Sanyal (sumana@wi.mit.edu, 617-324-1751; laboratory of Hidde Ploegh)
Joseph Ashour (jashour@wi.mit.edu, 617-324-5316; laboratory of Hidde Ploegh)

Spring 2013. Wednesdays, 1 pm – 3 pm. (Class time is flexible.) Room 68-150.

Co-evolution and adaption between viruses and humans are often portrayed as a zero-sum biological arms race. Viruses enter host cells equipped with an array of mechanisms to evade the host defense responses and replicate. The rapid rate of mutation of viruses permits evolution of various methodologies for infection, which in turn drive development of non-specific but highly effective host mechanisms to restrict infection. This class will discuss the varied solutions each side has developed as a means for survival. Focus will be on protein-protein interactions, host mimicry, intra-cellular trafficking, hijacking of host-cell machinery and up-regulation of multiple signaling pathways and subsequent induction of antiviral proteins. We will use examples drawn from human disease-causing pathogens that contribute seriously to the global health burden, including HIV, influenza and dengue virus. Primary research papers will be discussed to help students learn to pose scientific questions and design and conduct experiments to answer the questions and critically interpret data. We will visit a local biotechnology company to learn how the knowledge and techniques discussed in class are being applied towards vaccine development.