Advanced Undergraduate Seminars
2011-2012

Fall 2011

7.341 Metastasis: The Deadly Spread of Cancer

Instructors: John Lamar (lamarj@mit.edu, 452-2769; laboratory of Richard Hynes)
Amy McMahon (mcmahona@mit.edu, 452-2769; laboratory of Richard Hynes)

Fall 2011. Thursdays, 11 am-1 pm. (class time is flexible). Room 68-150

Cancer is a devastating disease that kills millions of people every year. Greater then 90% of these deaths result from metastasis, the spread of cancerous cells from the initial tumor to other organs in the body. Metastasis is a complex cascade involving several essential cellular processes, such as migration, invasion, entering and exiting the bloodstream, survival, and growth. It is unclear how several of these processes are regulated during cancer progression, making metastasis an important area of research in cancer biology. In this course students will learn to critically evaluate primary research articles published in the field of cancer metastasis. We will discuss current theories about how cancer cells gain the ability to metastasize as well as how several of the critical processes involved in metastatic dissemination are regulated at a cellular level. We will investigate how metastasis can be influenced by the interaction of tumor cells with other cells in the body, including non-malignant cells present in the tumor, the bloodstream, and distant organs to which tumor cells metastasize. We will learn about existing therapies that target metastatic dissemination and explore how new therapies could be designed to target the processes and interactions discussed throughout the course. Emphasis will be placed on teaching students how to design and critique experiments and on learning about important techniques in the field. Refreshments will be provided during class. Students will visit a research facility and have the optional opportunity to attend research seminars presented by prominent scientists in the field.

7. 342 The Biology of Aging: Age-Related Diseases and Interventions

Instructors: Eric Bell (bearfan@mit.edu, 3-4768; laboratory of Lenny Guarente)
Dudley Lamming (dlamming@mit.edu, 2-1908; laboratory of David Sabatini)

Fall 2011. Wednesdays, 11 am-1 pm. (Class time is flexible.) Room 68-150.

Aging involves an intrinsic and progressive decline in function that eventually will affect us all. While everyone is familiar with aging, many basic questions about aging are mysterious. Why are older people more likely to experience diseases like cancer, stroke, and neurodegenerative disorders? What changes happen at the molecular and cellular levels to cause the changes that we associate with old age? Is aging itself a disease, and can we successfully intervene in the aging process? In this course, we will explore the scientific discoveries made from studies of model organisms, including yeast, worms, flies and mice, which have led to revelations about the molecular biology of aging. We will discuss calorie restriction, an intervention that extends the lifespan of organisms as

diverse as yeast and primates, and the implications for successfully intervening in age-related diseases. We will also discuss the first tests of drugs such as resveratrol (a small molecule found in red wine) and rapamycin, which may target aging pathways in mammals. We will participate in a field trip to a meeting of the Boston Area Aging Data Club, where we will meet the authors of some of the papers that we have covered in class and hear a presentation by a researcher actively working on a hot topic in the field of aging.

7.343 Cancer and Its (Micro)environment – from Basic Science to Therapy

Instructors: Julia Rastelli (rastelli@wi.mit.edu, 8-5173; laboratory of Bob Weinberg)
Asaf Spiegel (spiegel@wi.mit.edu, 8-5173; laboratory of Bob Weinberg)
Fall 2011. Mondays, 3-5 pm. (Class time is flexible.) Room 68-150.

Despite major advances in cancer research, the treatment of most cancers remains insufficient, rendering the disease a leading cause of death in the western world. Tumors are complex tissues that consist not only of malignant cells but also of a variety of non-malignant cells, such as blood vessel cells, immune cells, and fibroblasts (also called the tumor stroma). What is the role of these stromal cells in the tumor, and what is the normal physiological role of such cells in the human body? How are the fundamental steps of tumor progression, such as angiogenesis (blood vessel formation) and metastasis (spreading of tumor cells to distant tissues), affected by stromal cells? Is there heterogeneity even among the malignant cancer cells? And if so, are some of the cells better able to initiate a tumor and can such cells be considered cancer stem cells?

In this course we will discuss and critically evaluate scientific papers that attempt to answer these questions in one of the most exciting and rapidly evolving fields in cancer research – the tumor (micro)environment. We will also discuss how non-malignant tumor cells might be used as new targets for cancer therapy as a complement to conventional therapy based on targeting only the malignant cells.

7.344 Biological Networks: Using Hairballs to Study Genes, Pathways and Diseases

Instructor: Igor Ulitsky (ulitskyi@gmail.com, 8-8346; laboratory of David Bartel)
Fall 2011. Tuesdays, 11 am – 1 pm. (Class time is flexible.) Room 68-150.

What do Facebook, the human brain and the electricity grid have in common with transcriptional regulation in a cell? One simple answer is that they can all be represented as networks. Visually, these networks appear to be uninterpretable 'hairballs,' but in fact, studying their structures and features can help us understand the principles of these complex systems. Although networks from entirely different domains share surprising similarities, biological networks also have their own unique characteristics. Analysis of these networks involves using established techniques from statistics, computer science and physics as well as methods developed specifically for studying systems biology. In this course we will introduce various biological networks, discuss methods for their analysis and witness how network-based approaches are advancing various areas of biomedical research. We will begin by presenting the basic principles of network

structures. We will then cover many of the basic molecular interaction networks studied in biology, including those of protein-protein interactions, transcriptional regulation, metabolic reactions, genetic interactions, drug-target interactions and others. We will see how high-throughput experiments provide data that can be conceptualized as networks. We will present models and algorithms used to study networks at different resolutions, and what insights can be derived from this analysis. Furthermore, we will discuss specific questions that can be answered by understanding networks: how can we use networks to predict which genes are responsible for a specific disease? what is the best way to perturb a network to escape from a disease state? how can we identify drugs that share a mode of action using networks? This course will not require any expert knowledge in biology, computer science or statistics.

7.345 Making a Nervous System: Processes, Problems, and Human Disorders

Instructors: Alicia Blaker-Lee (blaker@wi.mit.edu, 8-5200; laboratory of Hazel Sive)
Jasmine McCammon (mccammon@wi.mit.edu, 8-5200; laboratory of Hazel Sive)

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

The embryo undergoes a symphony of well-orchestrated events to develop a functional nervous system. A mistake at any one of many levels can result in serious defects, ranging from a mild form of a mental health disorder to a severe neural tube defect. Such abnormalities can have a distressing impact on the patient's quality of life and even on survival. In this course we will discuss many aspects of normal nervous system development and address the etiology of human nervous system disorders. Specific topics will include mental health disorders, such as schizophrenia and autism, and neural tube closure defects, such as spina bifida and exencephaly. We will discuss the latest approaches that scientists are using to address the following questions: How do improper neural tube formation, synapse formation, and neural connections contribute to these maladies? What genes or pathways are involved in these processes? What are the tools and animal models best suited to study these disorders? This course will rely on reading and analyzing primary research articles to discuss experimental design as well as interpretation and application of the data.

7.346 Cellular Garbage Disposal: Misfolded Proteins in Normal Biology and Human Disease

Instructor: Sumana Sanyal (sumana@wi.mit.edu, 4-1751; laboratory of Hidde Ploegh)

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

The endoplasmic reticulum (ER) orchestrates different cellular processes by which proteins are synthesized, correctly folded, modified and ultimately transported to their final destinations. As part of this crucial biosynthetic process, proteins that are not properly folded and consequently detrimental to normal cellular function are constantly generated. A common signature of many neurodegenerative diseases, including Alzheimer's and Parkinson's, is accumulation and deposition of misfolded proteins that

arise when the ability of cells to deal with the burden of misfolded proteins is compromised. In this course, we will explore how the ER quality control machinery ensures that only properly assembled proteins exit the ER while distinguishing between nascent proteins *en route* to their biologically active folded state from those that are terminally misfolded. The flux through the ER involves a repertoire of proteins with varying physical characteristics including soluble, membrane-bound and lipid-anchored proteins. We will discuss how such distinct cargo proteins are recognized, transported from the ER to the cytosol and ultimately degraded by proteasomes. Tools and approaches used to delineate underlying molecular mechanisms of the pathway, emerging concepts of specificity regarding substrate selection, possible modes of transport across the ER bilayer, maintenance in a soluble form once in the cytosol and the role of ubiquitylation in proteasomal degradation will be addressed.

Spring 2012

7.341 Molecularly Targeted Therapies in Blood Disorders and Malignancy
Instructors: Bill Wong (pwong@wi.mit.edu, 650-799-8364; laboratory of Harvey Lodish)
Spring 2012. Wednesdays, 3 – 5 pm. Room 68-150. (Class time and venue is subject to change based on enrolled students' schedules.)

How are new drugs and treatments discovered? This course will take you from the discoveries of basic research to the customized design of drugs for treating patients with specific deadly blood disorders. Students will experience the scientific journey from the rationale of the scientists who started basic research projects to that of the clinicians who designed the trials to test the safety and efficacy of prospective drugs. We will consider the scientific discoveries that led to development of Gleevec, which is often referred as a miracle drug or silver bullet for a specific leukemia, chronic myelogenous leukemia. Gleevec was developed based on the principle of molecularly targeting an abnormal kinase activity encoded by an oncogene and in this way killing leukemia cells while leaving normal cells alone. The following topics will be discussed: (1) identification of a bcr-abl chromosomal translocation and demonstration that this translocation generates an abnormal kinase activity that causes leukemia, (2) drug design and efficacy and toxicity testing in mice and humans, (3) mechanisms of drug resistance and finally, (4) uses of Gleevec in other diseases that also abnormally express the oncogenic abl kinase. We will also discuss other topics that demonstrate the process from "bench to bedside," such as stem cell and gene therapy, the design of drugs based on RNA interference, and the reprogramming of somatic cells into stem cells for regenerative medicine.

7.342 Regenerative Medicine: from Bench to Bedside and Bedside to Bench

Instructors: Petra Simic (psimic@mit.edu, 3-0809; laboratory of Leonard Guarente)
Jana Hersch (jhersch@alum.mit.edu, 617-710-3496; laboratory of Peter Reddien)

Spring 2012. Wednesdays, 1 pm – 3 pm. (Class time is flexible.) Room 68-150.

Regenerative medicine involves the repair and regeneration of tissues for therapeutic purposes, such as replacing bone marrow in leukemia, cartilage in osteoarthritis or cells of the heart after a heart attack. Tissue regeneration has been of interest throughout history. There is even a Greek myth that describes liver regeneration: Prometheus was chained to a mountain, and his liver was eaten daily by an eagle, regenerated and then eaten again the next day. Today advances in basic and clinical research make tissue regeneration feasible. In humans, tissue is normally generated during fetal development by the differentiation of embryonic stem cells or during postnatal life by a similar differentiation of adult stem cells. Regenerative medicine tries to mimic these processes. In this class, we will explore basic mechanisms of how cells in a variety of organisms differentiate into specific tissues in response to biologic stimuli and how these findings have been used to advance regenerative medicine for humans. We will discuss the use of biologic factors for *in vitro* tissue production. For example, bone morphogenetic proteins can be used *in vitro* to drive the differentiation of adult stem cells towards bone and heart. We will also study the cellular mechanisms involved in the cloning of animals and how Scottish researchers produced the sheep Dolly using the nucleus of a mammary gland cell from an adult sheep. We will read papers describing organ production, such as the *in vitro* formation of beating heart cells. We will also consider the molecular bases of cellular and functional changes of different organs that occur in disease and treatments that can cause tissue remodeling to correct these changes. We will discuss how studies of the developmental, cellular and molecular biology of regeneration have led to the discovery of new drugs. We will visit the Massachusetts General Hospital to see the patients with regenerated tissues.

7.343 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)

Spring 2012. Wednesdays, 11 am – 1 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 mitochondria from malfunctioning. Lastly, we will learn about the molecular mechanics of defective mitochondria that have been identified in human diseases.

7.344 The Evolutionary Basis of Human Biology

Instructor: Mansi Srivastava (mansi@wi.mit.edu, 4-2147; laboratory of Peter Reddien)
Spring 2012. Thursdays 1 pm – 3 pm. (Class time is flexible.) Room 68-150.

We are all products of evolution. If we aim to understand human biology – our traits, genes, development, and diseases – we must study our biology in the context of our evolutionary history. For instance, how does the 4% difference between our genome and the chimp genome make us human? The question of what defines us as humans is beginning to be answered in unprecedented ways using technologies developed in the past decade. In this course, we will explore a diverse range of topics, including comparative genomics, evolutionary developmental biology, and population genetics, by discussing primary research papers highlighting fundamental insights that an evolutionary perspective has brought to human biology. We will begin by placing humans in the context of other animals and simpler eukaryotes to establish a framework for the discussions to follow. We will then focus on various aspects of human biology through the lens of evolution. We will examine the past to understand the origins of the molecular underpinnings of key features of human biology. We will also look to the future for potential applications of the evolutionary knowledge we have acquired – for example, can we find better models of human disease given our evolutionary relationships with other organisms?

7.345 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)
Spring 2012. Fridays, 11 am – 1 pm. (Class time is flexible.) Room 68-150.

Every time we scientists think that we have dissected the precise biological nature of a process, an incidental finding, a brilliantly designed experiment, or an unexpected result can turn our world upside down. Non-coding RNAs, discovered through both luck and perseverance, are striking examples of this concept. Until recently thought by many to be cellular "junk" because they do not encode proteins, non-coding RNAs are gaining a growing recognition for their roles in the regulation of a wide scope of processes, ranging

from embryogenesis and development to cancer and degenerative disorders. The aim of this class is to introduce the diversity of the RNA world, inhabited by microRNAs, lincRNAs, piRNAs, and many others. Our goal is to glean insights into the functional importance of these RNA molecules and to understand the mechanisms of their action. We will discuss landmark studies that offer a historical perspective as well as read papers from the latest issues of scientific journals to learn about the most recent developments in this rapidly evolving field. We will discover how changes in non-coding RNAs can lead to disease and how we can explore the therapeutic potential of non-coding RNAs.

7.346 Antibiotics, Toxins, Protein Engineering and The Ribosome: Science at the Interface of Biology, Chemistry, Bioengineering, and Medicine

Instructor: Caroline Koehrer (koehrer@mit.edu, 3-1870; laboratory of Uttam L. RajBhandary)

Spring 2012. Thursdays, 11 am – 1 pm. (Day and time are flexible.) Room 68-150.

According to the Centers for Disease Control (CDC), in the year 2008, MRSA (Methicillin Resistant *Staphylococcus aureus)* was responsible for an estimated 90,000 invasive life-threatening infections and more than 15,000 deaths in the U.S. After decades of widespread use, many antibiotics are not as effective as they used to be. Resistance to commonly used antibiotics and the surfacing of multidrug-resistant microbes – so called *superbugs* – have become one of the world's most pressing public health problems. Did you know that many of the widely used antibiotics such as tetracyclines, aminoglycosides and macrolides; the lethal poison Ricin, best known as a weapon of bioterrorism; and *Diphtheria* toxin, the causative agent of a highly contagious bacterial disease – all have one thing in common: they specifically target the cell's translational apparatus and disrupt protein synthesis. In this course, we will discuss the structure and function of the ribosome and look into the most basic concepts of protein synthesis? We will explore the mechanisms of action of antibiotics and toxins targeting the translational machinery, their roles in everyday medicine, and the emergence and spread of drug resistance. We will also discuss the identification of new drug targets and how we can manipulate the cell's protein synthesis machinery to provide powerful tools for protein engineering and potential new treatments for patients with devastating diseases, such as cystic fibrosis and muscular dystrophy.