

**Advanced Undergraduate Seminars
2009-2010**

Fall 2009

7.340 Learning and Memory: The Activity of the Nervous System Controls Gene Expression To Shape the Biology of the Brain

Instructor: Sven Loebrich (loebrich@mit.edu, 8-5241; laboratory of Elly Nedivi)
Fall 2009. Mondays, 1 – 3 pm. (Class time is flexible.) Room 68-151.

The mammalian brain easily outperforms any man-made supercomputer with respect to computing time and process complexity. The brain adapts and changes constantly in response to external stimuli. Most importantly, the brain enables us to continuously learn and remember new things. A single experience, such as touching a hot plate, witnessing a tragedy, or experiencing the shocking taste of durian fruit can be remembered for life. What are the molecular mechanisms that lead to learning and memory? How do nerve cells, inter-neural connections (synapses) and brain circuits change over time to store information? Electrical activity in the nervous system controls the expression of a set of genes that can affect neuronal function. What are the cellular roles that activity-regulated gene products play to implement changes in the brain? We will discuss the molecular mechanisms of such neuronal plasticity at the synaptic, neuronal and circuit levels. We will consider fundamental neurobiological processes, such as (1) synapse formation, (2) synaptic growth and stabilization, (3) synaptic transmission, (4) axonal and dendritic outgrowth, and (5) circuit formation, with some focus on the visual system. We will learn about the roles of some activity-regulated genes in these processes, and we will study their functions in various experimental systems, such as dissociated neuronal cultures, cultured brain slices, and the living brain. In addition, we will learn about the tools and techniques employed in modern neuroscience research. Our goal will be to understand molecular mechanisms the brain employs to bring about the complex phenomena of learning and memory.

7.341 Bench to Bedside: Molecularly Targeted Therapies in Blood Disorders and Malignancy

Instructors: Johan Flygare (flygare@wi.mit.edu, 2-5227; laboratory of Harvey Lodish)
Bill Wong (pwong@wi.mit.edu, 650-799-8364; laboratory of Harvey Lodish)
Fall 2009. Wednesdays, 3 – 5 pm. (Class time is flexible.) Room 68-151.

Where do new drugs and treatments come from? This class will take you from the test tubes and mice of the laboratory to the treatment of patients with deadly blood disorders. Students will learn how to think as a scientist by discussing primary research papers describing the discoveries of several novel treatments from the perspectives of a basic scientist, the pharmaceutical industry and a practicing clinician. Topics such as gene therapy, the potential of drugs based on RNA interference and the reprogramming of somatic cells into stem cells for regenerative medicine will be discussed. We will consider in depth the leukemia drug Gleevec, which is often referred to as a miracle drug

or silver bullet. This drug is used to treat chronic myelogenous leukemia (CML) and kills leukemic cells while normal cells are left alone by targeting an oncogenic protein that exists in only the leukemic cells. The unprecedented success of this drug's achieving 90% efficacy in patients depended strongly on basic research: first an abnormal chromosome was discovered, then the exact genetic defect -- bcr-abl chromosomal translocation -- was identified, the abnormal kinase activity encoded by the bcr-abl fusion genes was shown to be the cause of the leukemia and then a specific inhibitor of this kinase was developed. This striking success increased the rationale for bringing 'bench' discoveries to the 'bedside.' We will discuss issues involved in drug development, such as lead compound discovery, modification through medicinal chemistry and efficacy and toxicity testing *in vitro*, in animal models and eventually in humans in large-scale clinical trials. Just as bacteria can develop resistance to antibiotics, leukemic cells similarly can evolve mechanisms to evade the therapeutic effects of Gleevec. Strategies will be discussed to attack Gleevec-resistant leukemic cells. Finally, we will explore the uses of Gleevec in diseases other than CML that constitutively express the oncogenic Abl kinase or other kinases that have proven also to be inhibited by Gleevec

7.342 The X in Sex: A Genetic, Medical, and Evolutionary View of the X Chromosome

Instructor: Jacob Mueller (jmueller@wi.mit.edu, 254-8420; laboratory of David Page)
Fall 2009. Thursdays, 1-3 pm. (Class time is flexible.) Room 68-151.

What do colorblindness, Queen Victoria, and ligers (hybrids generated by male lions and female tigers) have to do with the X chromosome? This course will explore a diverse collection of striking biological phenomena associated with the X chromosome. The X chromosome is the most intensively studied chromosome in medical genetics; genes for over 300 diseases have been mapped to it. We will examine the genetic basis and significance of several X-linked mutations (e.g. the mutation proving the chromosome theory of inheritance and mutations that cause sex reversal). We will also discuss why men are more likely than women to display X-linked traits. This X-inequality between the sexes (XY males, XX females) raises an important biological question: how do males, with their single X chromosome per cell, and females, with two, balance their relative levels of X-linked gene expression? We will look at the different mechanisms by which X chromosome gene expression is equalized in mammals, flies, and worms and how these mechanisms can yield unusual phenotypes, such as calico cats, almost all of which are female. We will also discuss the evolutionary history of the X chromosome, considering questions such as: how did the X and Y chromosomes evolve from an ordinary pair of autosomes? what role do X-linked genes play in the male sterility of hybrid organisms, such as ligers, mules or zorses? and what can the X chromosome tell us about the speciation of humans? Throughout our discussions of the X chromosome we will use both recent and classic primary research papers to learn about this chromosome's fascinating biology.

7.343 When Development Goes Crazy: How Cancer Co-opts Mechanisms of Embryogenesis

Instructors: Trudy Oliver (tgo@mit.edu; 8-6789; laboratory of Tyler Jacks)

Etienne Meylan (emeylan@mit.edu; 2-3821; laboratory of Tyler Jacks)

Fall 2009. Thursdays, 3 – 5 pm. (Class time is flexible.) Room 68-151.

Cancer is a leading cause of death worldwide. Few treatment options exist, most of which rely on a single characteristic of cancer cells—their increased proliferation rate. Treatment with traditional therapies, such as radiation or chemotherapy, can be highly toxic, and patients often experience relapse as cancers acquire mutations that confer drug resistance. More effective cancer therapies are very much needed. Such therapies are now being developed based upon an understanding of cancer biology, which in many ways involves dysregulation of the normal biology of development. During human embryonic development, a single cell—the fertilized egg—divides and its descendants grow, differentiate, and assemble to generate a highly complex human being. Throughout these developmental processes, cells communicate with each other via complex signaling networks composed of proteins interacting with other proteins. Signaling pathways that drive development have been identified, and, strikingly, many of them are altered in cancer. Cancer involves uncontrolled cell growth, failure to differentiate into a particular cell type, resistance to cell death, increased cellular motility, and formation of new blood vessels. All of these processes are utilized during development, and all are misused in cancer.

During this course, we will study the similarities between cancer and normal development to understand how tumors co-opt developmental processes to facilitate cancer initiation, maintenance and progression. We will examine critical signaling pathways that govern these processes and, importantly, how some of these pathways hold promise as therapeutic targets for cancer treatment. We will discuss how future treatments might be personalized to target cancer cells in specific patients. We will also consider examples of newly-approved drugs that have dramatically helped patients combat this devastating disease.

7.344 The Biology and Diseases of Aging

Instructors: Michael Bonkowski (mbonkows@mit.edu, 68-295; laboratory of Lenny Guarente)

Dena Cohen (greenrna@mit.edu, 68-294; laboratory of Lenny Guarente)

Fall 2009. Thursdays, 11 am – 1 pm. (Class time is flexible.) Room 68-151.

Aging is a familiar yet mysterious aspect of human biology. Why are older people so much more likely to develop diseases like osteoporosis, stroke, and neurodegenerative disorders? Is aging itself a disease? What changes happen at the molecular and cellular levels that cause the changes that we associate with old age? Can changing the nutrient balance of the human diet extend lifespan? To this day, the specific molecular causes of aging remain poorly defined. Common laboratory organisms such as yeast, the roundworm *C. elegans*, and mice undergo aging, and scientists have studied these organisms to try to unlock the mysteries of the aging process. For all of these organisms, mutations have been identified that slow aging, allowing the organism to live up to ten

times as long as normal. The finding that aging can be controlled by individual genes has led to the exciting idea that drugs might be developed to intervene with the actions of such genes, slow the aging process and delay the onset of all of the diseases of aging in humans. In this course, we will explore the scientific discoveries that have led to various theories of the molecular basis of aging. We will study the shared genetic pathways that control lifespan in organisms as different from each other as yeast and mice. We will also discuss the first tests of drugs such as resveratrol, a small molecule found in red wine, that 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 aging field.

7.345 Vascular Development in Life, Disease and Cancer Medicine

Instructor: Alexandra Naba (anaba@mit.edu, 3-6424; laboratory of Richard Hynes)

Christopher Turner (turnercj@mit.edu, 3-6409; laboratory of Richard Hynes)

Fall 2009. Wednesdays, 1-3 pm. (Class time flexible.) Room 68-151.

The growth of blood vessels, a process known as angiogenesis, is one of the earliest events in mammalian development and is regulated by a sensitive interplay of growth factors and other molecules. Abnormal or excessive angiogenesis occurs in diseases that include cancer, diabetes and atherosclerosis, whereas insufficient angiogenesis or vessel regression can lead to Alzheimer's disease, ischemic heart disease and impaired wound healing. For this reason, more than \$4 billion dollars has been invested in research and development to identify medicines that either promote or reduce the growth of new blood vessels, making angiogenesis one of the most exciting and heavily funded research areas in biomedicine today. In this course, we will discuss the key molecular regulators of blood vessel development as well as the techniques and experimental systems that have been utilized by vascular biologists. Emphasis will be given to the recent progress made in the microscopic visualization of blood vessels and live cell and intravital imaging used for diagnosis in the clinic. We will also examine the success of several anti-angiogenic treatments that have been approved by the Food and Drug Administration (FDA), that inhibit the pro-angiogenic vascular endothelial growth factor, VEGF, and that are now being used to treat age-related macular degeneration. Finally, we will explore how during the course of cancer progression, establishment of a blood supply into a tumor can lead to the growth and spread of cancer cells to secondary sites. We will discuss the caveats and potential pitfalls of targeting tumor blood vessels to starve cancer cells and prevent the spread of cancer, which remains one of the leading causes of death in the USA.

Spring 2010

7.346 RNAi: A Revolution in Biology and Therapeutics

Instructors: Allan Gurtan (gurtan@mit.edu, 3-6458; laboratory of Phillip Sharp)

Michael Goldberg (michaelg@mit.edu, 3-6457; laboratory of Phillip Sharp)

Spring 2010. Thursdays, 3 pm – 5 pm. (Class time is flexible.) Room 68-151.

The goal of medicine is to cure disease. Despite centuries of effort, however, modern medicine struggles against the same obstacles today as medicine did in its early days: identifying the cause of a disease and treating it specifically without inducing side effects. While significant advances in medicinal chemistry have been made over many decades, traditional small molecule therapeutics remain unpredictable, often because of a lack of specificity. Similarly, the recent advent of recombinant DNA technology, though ushering in an era of protein-based therapeutics, has achieved only limited success, owing in part to difficulties posed by the large sizes of these macromolecules. What, then, is the next therapeutic frontier? The answer may lie in RNA interference (RNAi), a fundamental biological process discovered only a decade ago and recognized soon afterwards with the 2006 Nobel Prize in Physiology or Medicine. RNAi is mediated by small interfering RNAs (siRNAs), which direct the efficient degradation of specific messenger RNAs, thereby inhibiting the synthesis of specific proteins. Since its discovery, RNAi has revolutionized basic science research by allowing analyses of the genes and proteins required for cellular processes. RNAi can be used to test candidate disease target genes in cellular and animal models of human disease. Additionally, the race is now on to develop siRNAs as a class of therapeutic agents. In principle, any gene known to play an essential role in a disease pathway can be targeted by RNAi. In this course, we will discuss the studies that have led to the current excitement concerning the therapeutic potential of this new field. Specifically, we will consider various aspects of RNAi: its discovery, how it functions in normal biological processes, its utility as an experimental tool, its potential for therapeutic use, and how RNAi therapeutics are being pursued by the biotechnology industry.

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

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

Spring 2010. Thursdays, 1 – 3 pm. (Class time is flexible.) Room 68-151.

The lethal poison Ricin, best known as a weapon of bioterrorism; *Diphtheria* toxin, the causative agent of a highly contagious bacterial disease; and the widely used antibiotic tetracycline – all three have one thing in common: they specifically target the cell's translational apparatus and disrupt protein synthesis. In this course, we will explore the mechanisms of action of toxins and antibiotics, 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 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.

7.348 Non-malignant Tumor Cells – A Broader Approach to Cancer Research

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)

Spring 2009. Wednesdays, 3-5 pm. (Class time is flexible.) Room 68-151.

Despite 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 stromal cells, such as blood vessel cells, immune cells, and fibroblasts. What is the role of stromal cells in the tumor, and what is the normal physiological role of such cells in the human body? Where do stromal cells come from, and what triggers their recruitment into tumors? How do stromal cells affect the fundamental steps of tumor progression, such as angiogenesis (blood vessel formation) and metastasis (spreading of tumor cells to distant tissues)? 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.

7.349 From Molecules to Behavior: Synaptic Neurophysiology

Instructor: Alex Chubykin (chubykin@mit.edu; 46-3301; laboratory of Mark Bear)

Spring 2010. Wednesdays, 11 am – 1 pm. (Class time is flexible.) Room 68-151.

The brain is the most sophisticated computational machine known. Vastly different from conventional man-made computers, the brain is massively parallel, self-organizing, and plastic - it can change its own components and rewire itself to a new configuration necessary for a new task. Synapses, the connections between nerve cells, are the fundamental computational units of the brain. Like transistors in a computer, synapses perform complex computations and connect the brain's non-linear processing elements (neurons) into a functional circuit. Understanding the role of synapses in neuronal computation is essential to understanding how the brain works. In this course students will be introduced to cutting-edge research in the field of synaptic neurophysiology. The course will cover such topics as synapse formation, synaptic function, synaptic plasticity, the roles of synapses in higher cognitive processes and how synaptic dysfunction can lead to disease. This research requires a wide range of techniques, including molecular genetics, biochemistry, electrophysiology and optical imaging, and examines mechanisms involved in the development, physiology, and pathophysiology of the nervous system. We will read both classical research papers addressing the basics of synaptic physiology and the latest research papers addressing the role of synapses in the function of neuronal circuits. Students will learn to critically analyze scientific papers, to apply the scientific method in neuroscience research, to evaluate and interpret data and to design experiments.

7.340 Regenerative Medicine: from Bench to Bedside

Instructor: Petra Simic (psimic@mit.edu, 3-0809; laboratory of Lenny Guarente)
Spring 2010. Wednesdays, 1 pm – 3 pm. (Class time is flexible.) Room 68-151.

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. 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 course, we will explore basic mechanisms of how cells differentiate into specific tissues in response to a variety of biologic signaling molecules. We will discuss the use of such 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 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 and the Genzyme drug production facility to see how drugs are produced for human use.