An Introductory Biology Course, Framed with the Complete Plays of Shakespeare

1) Phylogenies, *The Tragedy of King Richard the Second*

The Tragedy of King Richard the Second documents a struggle for survival, played out between two descendants of Edward III. Henry, the victor, secures the throne for his son; Richard, the loser, dies childless. In this lecture, we examine similar struggles in nature, played out between species and individual organisms. We compare the Plantagenet family tree, grounded in a "most royal root," to the biological tree of life, rooted in a single universal ancestor. We see, in both cases, that many of the "branches...are dried by nature's course," either through accident or illness, or as driven by resource competition ("kin with kin and kind with kind confound"). We consider the role of extinction ("blotted from the book of life") in biological evolution, and describe the effects of mass extinctions at the end of the Permian and Cretaceous. We see how such events, by vacating old new niches, have helped shape the composition of future organisms, "yet unborn and unbegot." We place four early evolutionary events on an approximate timeline: the origin of life, the origin of photosynthesis, the origin of eukaryotes, and the origin of multicellularity. We see how these early events underlie current biodiversity, and describe the division of life into the Prokarya, Archaea, and Eukarya domains. We conclude by considering finer levels of categorization, from kingdom to species, with particular focus on divisions within eukaryotes.

2) Major Transitions in Vertebrate Evolution, *The Tempest*

In this lecture, we use *The Tempest* to examine two sea/land transitions in vertebrate evolution. We look first the evolution of tetrapods, as derived from fish. We parallel this transition with events in the play, as "sea-swallow'd" characters are conveyed to dry land. We look next at the evolution of cetaceans, as derived from land mammals. We also parallel this transition with events in *The Tempest*, as characters, much altered by their time on the island, consider a return to the sea ("sail so expeditious"). We discuss timescales, contrasting the approximately 300 million years that separate the origins of tetrapods and cetaceans, with the approximately "three hours" that separate parallel events in the play. We see that these temporal differences stem from the operation of very different mechanisms: random mutation, coupled with selection, as compared with human will. We emphasize the gradual and undirected nature of evolution, criticizing Caliban's assertion that men might be "turned to barnacles;" at the same time, we also review the use of fossil specimens ("strange fish") and molecular genetics. We discuss differences between life at sea and on land, requiring new approaches to locomotion, water use, and gas exchange. We see how, during both the tetrapod and cetacean transitions, the challenges of the new environment were met by co-opting structures adapted to the previous environment. We contextualize our discussion by means of briefer considerations of other important transitions, including the origins of vertebrates, reptiles, and mammals.

3) Plant and Animal Domestication, *The Taming of the Sh*rew

In this lecture, we discuss evolution on a smaller scale, examining a special subset of cases influenced by human selection. We focus on three stories: the derivation of dogs from the wolves, goldfish from carp, and maize from teosinte. We frame our discussion using themes from *The Taming of the Shrew*, in which Petruchio obtains a docile variant of the "mad and headstrong" Katharina. We compare the unnatural methods employed by Petruchio—changes in diet, clothes, perception of the sun and moon, etc.—with the unnatural selection pressures favored by breeders. We emphasize the role of pre-existing variation, which limits what the breeder may select for; we note, in parallel that Petruchio does not reprogram Katharina but instead exploits traits that are latent in her personality. We discuss the role of founder effects and small gene pools; we look also at inbreeding as a tool for trait fixation, which carries both risks and benefits. We look, finally, at how new technologies have begun to alter these old approaches, enabling directed gene changes and the combination of traits from multiple species.

4) Genotype and Phenotype, *Cymbeline*

In *Cymbeline*, two princes are stolen at infancy and raised in the wild. "Train'd up thus meanly," they display a mixture of behaviors, many of which evidence their "princely blood." In this lecture, we see how similar experiments, performed on laboratory animals, can be used to characterize the relationship between genes and environment. We consider a range of gene-influenced diseases, from hemophilia to cancer, and distinguish between cases in which the gene always confers the disease, and cases in which it merely confers a predisposition. We in addition discuss the role of external inputs like vitamins and developmental toxins, and see how they can influence the acquisition of different traits given identical genes. We look also at two examples in which environmental inputs serve as a trigger, committing an organism to one of two developmental programs: first, at the role of chemical cues in the control of queen/worker fate in social insects, and, second, at the role of temperature in sex determination in some reptiles. Finally, we define haploid and diploid organisms, and see that, in the latter, the presence of two alleles introduces a sort of competition, through which the effects of the weaker allele may be hidden. We rephrase this observation in terms of allelic notation, noting that AA and Aa individuals may possess different genes but exhibit the same trait.

5) Hybrids and Mendelian Genetics, *The Tragedy of King Richard the Third*

In *The Tragedy of King Richard the Third*, peace is finalized by the marriage of Henry VII (House of Lancaster) and Elizabeth (House of York). This "fair conjunction" is symbolized by combining the roses—red and white—that symbolize the two houses. The resulting rose, a political hybrid, serves as the emblem of a new dynasty. In this lecture, we examine the genetics of the Lancaster-York hybrid, charting its genotype in the F1 and F2 generations. We in addition speculate on possible color phenotypes, assuming (a) dominant, or (b) semi-dominant inheritance. We see how these models of inheritance are

grounded in Mendel's *Pisum* experiments (as refined by later researchers) and briefly examine patterns (e.g., 9:3:3:1) observed during the segregation of multiple loci. We transition, finally, to efforts to combine more distantly related organisms, which we contextualize in terms of the chemistry that underlies reproduction. We look both at the chemistry of gamete fusion, which affects fertility in the first hybrid generation, and at the chemistry of gamete formation, which affects fertility in the second hybrid generation. We conclude with a survey of popular hybrids, including mules and wholphins, and discuss imprinting-based differences between ligers and tigons.

6) Mating Rituals, *Two Noble Kinsmen*

In *Two Noble Kinsmen*, cousins Palamon and Arcite compete for the hand of Princess Emilia. This competition is elaborate and stylized. A special venue is constructed ("I'll plant a pyramid") and six additional combatants are recruited. This "fair and knightly" competition is in addition prefaced by appeals to Mars and Venus ("Let the temples burn bright with sacred fires"). In this lecture, we examine comparable rituals in nature, similarly aimed at obtaining a reproductive partner. We begin with examples in birds, looking at the role of song and color display. We also describe the use of food presents ("I would bring her fruit fit for the gods to feed on...And then I am sure she would love me"), broadening our discussion to include additional species. We survey examples of mate competition ("our argument is love"), drawing parallels with the violence between Palamon and Arcite ("I am persuaded this question, sick between's, by bleeding must be cured"). We discuss tradeoffs between reproduction and individual survival in terms of energy investment; we note, however, that, in evolutionary terms, individual survival is irrelevant in the absence of reproduction ("no issue know us; no figures of ourselves shall we e'er see"). We see that these types of tradeoffs becomes more severe in sexual reproduction, as compared to asexual reproduction, as it becomes necessary not merely to nourish offspring but also to obtain mates ("this daring deed of fate in wedlock"). We conclude by observing that selective pressures to obtain mates can favor the possession of extreme characteristics, some of which can compromise survival.

7) Hermaphroditism, *Twelfth Night*

In *Twelfth Night*, Viola, a gentlewoman, acts as "both...a maid and man." At the beginning of the play, she assumes a masculine identity, adopting new clothes and a new name. With this "usurp'd attire," she obtains the love of Countess Olivia. Later, reassuming a female identity ("my maiden weeds"), she obtains the love of Duke Orsino. In this lecture, we examine a range of hermaphroditic strategies, adopted by species in nature. We look first at sequential hermaphrodites, which we further subdivide into protogynous and protoandrous species; we look also at simultaneous hermaphrodites, which we further subdivide into out-breeders and self-fertilizers. We contextualize these strategies in evolutionary terms, discussing advantages and disadvantages with respect to gonochorism. We conclude by examining the operation of self-incompatibility loci in hermaphroditic angiosperms, and describe their use as a barrier to inbreeding.

8) Embryonic Development, *Titus Andronicus*

In this lecture, we use *Titus Andronicus* to introduce embryonic development. We examine physical links between the queen, Tamora, and her several sons: Demetrius and Charon, whom she unwittingly devours ("eating the flesh that she herself hath bred"), and an unnamed newborn, conceived during an adulterous affair. We contrast mechanisms of nutrition delivery in egg-laying species, like birds and reptiles, with those of mammals, who are "sensibly fed of that self-blood." We describe early developmental phases, from fertilization to gastrulation, and define divisions between protostomes and deuterostomes. We conclude with a discussion of vertebrate limb formation, whilst referencing the importance of limbs (and violent limb removal) in the play.

9) Offspring Dispersal, *The Winter's Tale*

In this lecture, we use *The Winter's Tale* to frame comparisons between r- and K-selected species. We contrast the offspring care strategy of the King of Sicilia, who abandons his infant daughter to the elements, with that of the King of Bohemia, who retains and nurtures his son to adulthood. We discuss the pros and cons of each strategy, in terms of efficient energy investment, and examine environmental conditions that might favor one strategy over the other. We in addition examine the mechanics of offspring dispersal, as mediated by wind or water, or aided by other species.

10) Metamorphosis, *Coriolanus*

Coriolanus describes three stages in the development of a Roman soldier. Coriolanus is first Rome's champion ("in my country's service"), then its enemy ("My birth-place hate I"), and finally a broker of a Roman-Volscian peace ("I cannot make true wars"). In this lecture, we examine similarly dramatic transitions in nature, occurring during post-embryonic development. We begin by examining examples in holometabolous insects, tracking their conversions from larva to adult. We in addition examine functionally similar conversions occurring in amphibians. In each case, we highlight the importance of cell death during developmental remodeling, as juvenile structures are eliminated. Finally, we examine these life cycles in strategic terms, and discuss factors that may have favored their independent evolution in separate phyla.

11) Plant Pigments, *The First Part of King Henry the Sixth*

In *The First Part of King Henry the Sixth*, roses are used to symbolize political affiliation. Lancastrians adopt the red rose; Yorkists adopt the white. As tensions mount, these color differences are used to frame a range of insults. While the red roses "blush for pure shame," the white roses are "pale...with fear." In this lecture, we discuss the biochemical basis for differences in petal color. We examine the synthesis and deposition of floral pigments, using anthocyanin as our example. We in addition consider the adaptive value of color, noting its importance in many flower-pollinator relationships. We transition, finally, to a discussion of chlorophyll, which we define it in terms of its light absorption spectrum. We examine the role of chlorophyll in the leaf, and provide a preliminary sketch of photosynthesis.

12) Plant Senescence, *Othello*

In this lecture, we use *Othello* to discuss programmed death in plants. We look first at the murder of Desdemona, whom Othello compares to vegetation ("the rose...on the tree"). We see that Othello executes this murder precisely, determined to avoid the usual marks of violence. He will not "shed her blood" or "scar that...skin." We see that, in plants, senescence is undertaken via a similar precision, as energy stores ("vital growth") are carefully extracted from the dying cells, to be reused by the plant's remaining sections. We contrast this ordered disassembly with cell death occurring through necrosis. We discuss multiple senescence programs, ranging from the death of the entire plant, occurring in annuals, to the death of individual organs. We also discuss the importance of timing, both with respect to the season and with respect to developmental stage. We see that, just as the plant integrates external and internal cues, weighing whether to commit itself to a senescent program, Othello also integrates cues provided by Iago—balanced with his personal feelings—as he debates whether or not to kill Desdemona. We conclude by examining the practice of winter leaf abscission in deciduous trees, which we compare, in strategic terms, with leaf retention in evergreens.

13) Camouflage, *The Merchant of Venice*

In *The Merchant of Venice*, Portia, a wealthy heiress, adopts two disguises. The first is a lead casket. Enclosing her portrait, it protects her from the proposals of unworthy men. The second is a set of legal robes. Lending her the appearance of a "reverend doctor," it enables her to attack the "keen and greedy" Shylock. In this lecture, we look at the use of disguise in nature, both to avoid predators and to enable more effective predation. We discuss the chemistry of pigments, and examine the biology of chromatophores and melanocytes. We survey pigment-dependent patterns adopted by organisms in nature, enabling them to resemble their environments, and characterize these approaches in terms of timescale. We look at examples where external appearance is fixed, where it can be altered with respect to season, and where it can be altered rapidly. We in addition consider the use of conspicuous warning coloration, and discuss the evolutionary dynamics of Batesian mimicry. We look also at organisms with specialized disguise morphologies, enabling them to resemble uninteresting objects. We conclude by considering non-visual disguises, achieved through sound or smell.

14) Hibernation and Suspended Animation, *Romeo and Juliet*

In this lecture, we use *Romeo and Juliet* to examine the strategic adoption of "a thing like death." We begin by considering Juliet's use of "a sleeping potion" to avoid an unwanted marriage. We compare the slowing of Juliet's vital functions ("stiff and stark and cold") to the metabolic depression occurring during mammalian hibernation. We see that this state is similarly advantageous to the hibernating animals, enabling them to avoid the threat of winter starvation. We see that, like Juliet ("stifled in the vault"), many animals choose to occupy safe, cloistered spaces during their hibernation; also like Juliet, we see that their reawakening is plotted to coincide with the return of favorable conditions. We look also at similar themes operating during delayed seed germination in

plants. We characterize the plant embryo as existing in a latent state, anticipating changes that will enable it to emerge and resume rapid growth. We in addition parallel Juliet's deep sleep with the adoption of more extreme death-like states ("no pulse...no warmth, no breath") and discuss the formation of resistant spores in some bacterial species. We observe, finally, that laboratory researchers are able to impose a similarly quiescent state ("unnatural sleep"), in order to store cell stocks and embryos over the long term.

15) Parasitism, *Timon of Athens*

In this lecture, we use *Timon of Athens* to discuss interspecies relationships. We begin by examining the inequitable relationship between Timon, a wealthy landowner, and his "monstrous friends." We compare the transfer of resources ("the great shower of your gifts") from Timon to his friends to the transfer of resources from a host to parasite, which is similarly unidirectional. We examine a range of biological parasites, describing examples that kill their host and others that merely weaken them. We in addition examine the relationship between predator and prey, characterizing it in terms of the more overt threat posed to Athens by Alcibiades ("hostile strokes"/"terrible approach"). We transition, finally, to consider relationships that are mutually beneficial ("like brothers, commanding one another's fortunes"), with particular focus on lichens. We conclude by characterizing a range of relationships between humans and their resident microorganisms: some harmful, some helpful, some neutral.

16) Nutrient Cycles, *Hamlet*

In this lecture, we use *Hamlet* to discuss the transfer of matter between species. We begin by reflecting on the death of great men, aided by Hamlet's speeches. In Act IV, we consider the decay of kings ("through the guts of a beggar") and the role of decomposers ("we fat ourselves for maggots"). In Act V, similarly, we "trace the noble dust" of Alexander the Great, documenting its return to "base uses." We reinterpret these transformations in metabolic terms, describing mechanisms of digestion and polymer reassembly. We broaden our discussion by considering the structure of food chains, looking at examples in both terrestrial and aquatic systems. We see that the inefficiency of energy transfer at each stage creates a pyramid-like structure, in which a large number of organisms at the bottom is required to support a small number of organisms at the top. We further contextualize these transfers in terms of the global carbon cycle, tracking the exhalation of carbon dioxide and its re-conversion to organic tissue via the action of primary producers. We diagram the global nitrogen cycle in similar terms, focusing on nitrogen fixation. We emphasize the role of prokaryotes in mediating the majority of these transformations; we see that, by contrast, the biochemistry of eukaryotes is quite limited. We conclude by introducing basic terms in chemistry, including reactant and product, and describe additional concepts that underlie oxidation-reduction reactions.

17) Enzymes, *Much Ado about Nothing*

In *Much Ado About Nothing*, Beatrice and Benedick engage in two types of relationships. At first, they are adversaries, engaged in a "merry war." Later, they confess a deep affection: "I will live in thy heart, die in thy lap, and be buried in thy eyes." The transition between these two relationships—otherwise improbable—is mediated by the intervention of two groups. Hero, Ursula, and Margaret act on Beatrice, constructing clever "traps;" Don Pedro, Claudio, and Leonato, similarly, act on Benedick, careful to "bait the hook well." In this lecture, we compare this transition, mediated by humans, to a biological reaction, mediated by enzymes. We sketch events in the play (Beatrice + Benedick Ý Beatrice-Bendick) onto a reaction diagram, and characterize the stabilities of reactant and product. We define the transition state and compare likely activation energies in the presence and absence of the Hero and Don Pedro catalysts. We repeat these sketches using examples of biological synthesis reactions, also of the form, A+B Ý AB. We introduce additional types of biological reactions, including displacement and decomposition reactions, and discuss the relationship between substrate concentration and reaction rate. We survey the structures of several protein enzymes, with focus on the active site, and describe their discovery and nomenclature. We conclude by examining the action of enzyme inhibitors, distinguishing between endogenous inhibitors, which serve regulatory functions, and foreign inhibitors, which serve as drugs or poisons.

18) ATP and Energy Production, *King Lear*

In *King Lear*, Goneril and Regan deliver fawning speeches ("I am alone felicitate in your dear highness' love...") in order to please their father. Each is rewarded with half the kingdom. Cordelia, by contrast, refuses to invest any effort ("I cannot heave my heart into my mouth"). She, commensurately, obtains nothing. In this lecture, we examine similar investment-output correlations in the biological cell. We characterize life as an energy expensive undertaking, aimed at avoiding equilibrium with the environment. We discuss the importance of membranes in maintaining chemical differences, both between the cell and its exterior, and within cellular organelles like the mitochondrion. We survey a range of energy-requiring processes, including ion pumps, and define ATP as the cell's energy currency. We discuss the relationship between energy and differences in concentration, and describe the use of a hydrogen ion gradient to power ATP synthase. We provide a non-detailed sketch of glucose metabolism, focusing in particular on electron harvest, and examine the use of these electrons to drive pumps in the mitochondria. We conclude by reflecting on themes of investment and yield, noting that ATP is itself required to generate the machinery (enzymes, electron carriers, etc.) required for ATP synthesis.

19) Photosynthesis, *The Life of King Henry the Eighth*

In *The Life of King Henry the Eighth*, the king's favor drives the political ascension of multiple characters. His displeasure, similarly, contributes to their deaths. In this lecture, we exploit a metaphor, introduced in the play, which equates the king with the sun ("That sun, I pray, may never set!"). We see that, just as the king's power supports a nation, the sun's power supports entire ecosystems. We also pursue this metaphor in terms of light

deprivation. We compare the illnesses suffered by Queen Katharine and Cardinal Wolsey when denied the king's favor, to the slow starvation suffered by a photosynthetic organism when held in the dark ("like the lily, that once was mistress of the field and flourish'd, I'll hang my head and perish"). Prefaced by this metaphor, we examine the chemistry of photosynthesis, extending our introduction from Lecture 11. We describe the chloroplast and its internal organization, drawing comparisons with the mitochondrion. We review the exploitation of light energy by photosystems I and II, as enabled by light harvesting pigments. We describe electron harvest and oxygen evolution; at the same time, we also trace the production of ATP and NADPH. We briefly sketch the Calvin cycle, in terms of the number of carbons; in particular, we emphasize the function of the enzyme RuBisCO, and the fact that subsequent steps require ATP and NADPH. We conclude by discussing the fates of sugars produced during photosynthesis, noting possible employment as an energy source (accompanied by a reconversion to CO_2), or as building blocks to create structural polymers (cellulose).

20) Replication, *The Comedy of Errors*

In *The Comedy of Errors*, a ship, "splitted in the midst," is divided into two equal parts. Each part contains one member of two sets of identical baby twins, Antipholus and Dromio, who are also identically named. This division sets the stage for a later reunion, marked by a series of identity mix-ups, in which "I was ta'en for him, and he for me." In this lecture, we define the term "genetically identical" and examine four processes that can create genetically identical forms. Emphasizing questions of scale—single cells vs. clumps of cells—we introduce mitosis, clonal budding, the fission of deuterostome embryos to create identical twins, and laboratory cloning. At the same time, we also discuss events at a molecular level, describing the chemistry of DNA and the rules that govern base pairing. We sketch, finally, the basics of DNA replication, as catalyzed by DNA polymerase.

21) The Central Dogma, Part 1: DNA, *Macbeth*

In this lecture, we use *Macbeth* to discuss genomic DNA. We begin with King Macbeth's reflection on dogs and dog types. We distinguish, as he does, between characteristics that define the species ("all by the name of dogs") and characteristics that define particular breeds and particular individuals ("the swift, the slow, the subtle"). We translate Macbeth's explanation for these differences—"the gift which bounteous nature hath in him closed"—into precise molecular terms. We examine the gene, defining its promoter and protein coding regions, and provide an introductory sketch of transcription and translation. We look at genome organization, contrasting the circular chromosomes of prokaryotes with the linear chromosomes of eukaryotes. We diagram the eukaryotic chromosome in additional detail, describing centromeres and telomeres; we in addition chart gene density, highlighting regions that are gene-rich and gene-poor. We survey, finally, vital statistics in a wide range of genomes, comparing number of chromosomes, number of genes, and number of base pairs.

22) The Central Dogma, Part 2: RNA, *Measure for Measure*

In *Measure for Measure*, Vienna is governed first by the Duke, later by Lord Angelo. Each chooses to enforce a different subset of the city's written laws. The Duke, in particular, ignores the crime of non-marital sex. Angelo, by contrast, is determined to enforce the "strong statutes" against it. In this lecture, we examine similarities between the law of Vienna and the biological genome. We characterize both as storage sites for possible programs, only a few of which will actually be used. We in addition compare Vienna's governors with biological transcription factors, noting that both are responsible for deciding which programs will be used and which neglected. Prefaced by these comparisons, we describe gene expression in molecular terms. We discuss the function of the promoter and the concept of promoter "strength;" we in addition describe the interaction of transcription factors with DNA via specialized binding domains. We examine the recruitment of RNA polymerase and the assembly of the mRNA polymer. At the same time, we also describe the chemistry of RNA with reference to DNA. We revisit differences between prokaryotes and eukaryotes, and describe, in eukaryotes, the practice of mRNA splicing and nuclear export.

23) The Central Dogma, Part 3: Protein, *The Life and Death of King John*

In this lecture, we use *The Life and Death of King John* to discuss proteins and protein translation. We introduce a three-part metaphor, comparing the king with DNA, his written commands with RNA, and the recipients of these commands—those who "bear out the deed"—with translated protein products. We look in particular at the king's issue of a physical "warrant" for his nephew's murder, which we parallel to mRNA transcription; we see, further, that this warrant directs the construction of a new role (assassin) which we parallel to mRNA translation. Within this framework, we characterize proteins as molecular servants, responsible for a range of functions, including structure, transport, and catalysis. We see that this functional versatility is derived from the amino acids, which we categorize in terms of their R-group chemistry. We examine the RNA codon table; at the same time, we also introduce the tRNA, and describe how its structure mediates a correspondence between amino acid and codon. Finally, we introduce the ribosome, and sketch the synthesis of protein polymers, as directed by mRNA.

24) Protein Trafficking, *Pericles*

In *Pericles*, characters travel to sites throughout the Mediterranean, conveyed by ship. Pericles, fleeing Tyre, "puts himself unto the shipman's toil." Thaisa, similarly, is carried from Pentapolis to Ephesus in two stages, first by "dancing boat" and later by coffin. Later in the play, "a crew of pirates" abducts Marina from Tarsus and deposits her at Mytilene. In this lecture, we examine similar journeys, undertaken by proteins in the cell. We compare coastal cities, bordering the Mediterranean, to cellular organelles, bordered by cytosol. We trace the movement of maturing proteins, beginning on the ribosome, and describe a typical journey through the ER and Golgi. We diagram co- and

post-translational events, including the addition of lipid or sugar moieties, and consider the problem of protein folding. We survey a range of possible protein destinations, and describe the role of membrane vesicles ("well-sailing ships"). We conclude by considering additional challenges posed by proteins that are membrane-embedded or membrane associated, and trace the maturation a seven-transmembrane receptor.

25) Protein Turnover, *A Midsummer Night's Dream*

A Midsummer Night's Dream contains a mini-drama, "Pyramus and Thisbe," occupying the middle of Act 5. In it, each character serves a brief role, followed by a defined exit. Moonshine, Lion and Wall deliver a few blunt lines ("All that I have to say, is...") before exiting abruptly. The titular characters, similarly, complete a "tedious brief" love scene before emphatically stabbing themselves. Explicit soliloquies ("Thus die I...die, die, die" and "Farewell...Adieu, adieu, adieu") lend additional emphasis. In this lecture, we examine the performance of cellular proteins, whose roles, similarly brief, are concluded with comparable drama. We discuss the importance of protein turnover, both in terms of housekeeping and in terms of regulation, of which we examine several examples. We reintroduce the peptide bond, and describe the action of proteases. We sketch the chemistry of ubiquitin and ubiquitin attachment; we in addition introduce the proteasome, characterizing the functions of the cap and core. We look also at protein degradation as it occurs in the lysosome. We conclude by examining the fate of amino acids liberated by degradation, noting that they may either be used in protein synthesis or, further metabolized, may serve a range of other functions.

26) Skeletons: Endo-, Exo-, and Cyto-, *The First Part of King Henry the Fourth*

In this lecture, we use *The First Part of King Henry the Fourth* to discuss structural materials. We begin by considering Falstaff's girdle, which shapes and supports his "fat paunch." This supportive frame in addition facilitates Falstaff's motion, enabling him, at times, to convey himself "nimbly" and with "quick dexterity." Prefaced by this example, we consider parallel tactics, employed by organisms in nature, who are similarly "all filled up with guts." We discuss a range of exoskeletons adopted by invertebrates, focusing on arthropod examples, and examine the chemistry of chitin. We in addition see that many exoskeletons must be periodically molted ("doff our easy robes") in order to accommodate the organism's growth. We transition to a different structural solution, employed by vertebrates, and examine the chemistry and morphology of bones. We see that bones serve not only in the support and protection of "all this flesh," but also in mineral storage and blood formation. We transition, finally, to consider additional structural solutions, occurring at the level of individual cells. We introduce the cytoskeleton, and summarize important roles in cell shape, cell movement and cell division. We divide the cytoskeletal components into three categories—actin filaments, intermediate filaments, and microtubules—and briefly sketch the mechanisms that govern their assembly.

27) Membrane Transport, *Troilus and Cressida*

In *Troilus and Cressida*, the walls of Troy serve as a barrier, protecting the city from the Greeks. Defined ports, heavily guarded, permit a limited interchange: Trojan soldiers can enter and exit freely, but foreigners are carefully screened. These restrictions in addition enable Troy to retain Helen, whose loss the "law of nature" would otherwise mandate ("Nature craves all dues be render'd to their owners"). In this lecture, we compare Troy to a biological cell and the city wall to the plasma membrane. We compare the movement of people in and out of Troy, mediated by gated doorways, to the movement of molecules in and out of the cell, mediated by channels and pumps. In this framework, we review electrochemical gradients, as introduced in Lecture 18, and distinguish between active and passive transport. We survey a range of transporters and enumerate the rules that govern their function. We illustrate the action of the antiporter ("in right great exchange") using events in the play, observing that, in Act IV, Antenor is able to enter Troy only on the condition that Cressida exits it. We conclude by discussing the action of the sodium potassium pump. We compare the cellular energy expended on these pumps—aimed at maintaining low internal sodium, high internal potassium—to the "hell of pain and world of charge" expended by Troy in order to retain Helen.

28) Signaling Cascades, *The Merry Wives of Windsor*

The Merry Wives of Windsor consists of multiple plots, complexly interconnected. Mistresses Ford and Page contrive three schemes to humiliate Falstaff ("thrown in the Thames"/ "beaten...into all the colours of the rainbow"/ "mock him home to Windsor"). Anne and Fenton, meanwhile, plot a secret marriage, at the same time forcing two unwanted suitors to elope with the wrong bride. A duel between Caius and Sir Hugh, similarly, is prevented through the interference of friends, who contrive to convey them to separate meeting places. The advancement of each of these plots requires elaborate inter-character communication, mediated by mouth or by letter. Some of these messages are passed along chains consisting of multiple characters (e.g., AnneÝFentonÝHostÝVicar), while others rely upon the assistance of specialized intermediary messengers, in the form of Mistress Quickly or the page Robin. In this lecture, we diagram the play in terms of mechanisms of information transfer, and compare it to similar diagrams describing information transfer in the biological cell. We trace multiple signaling pathways, beginning with the receipt of ligands by cellular receptors and culminating in the action of transcription factors. We introduce three receptor classes, the G-protein coupled, the tyrosine kinase, and the steroid hormone, and compare their mechanisms of action. We describe the chemistry of phosphorylation, noting that such modifications may alter protein conformation or binding site recognition; on a larger scale, we look also at the operation of kinase cascades. We conclude by characterizing the role of second messengers, of which we examine four examples: cAMP, as generated by adenyl cyclase; DAG and IP3, as generated by PLC; and Ca^{2+}, as released from stores in the ER.

29) Pheromones, *Love's Labour's Lost*

In *Love's Labour's Lost*, the King and his followers commit themselves to an asexual lifestyle ("to fast, to study, and to see no woman"). Later, influenced by the arrival of the

Princess and her waiting women, they adopt a sexual program ("resolve to woo"). In this lecture, we examine the transition from asexual to sexual reproduction in baker's yeast. We diagram the yeast life cycle, focusing on the haploid stage, and compare the a and alpha mating types to the two human sexes. We highlight the role of the mating pheromones, comparing them to the gifts ("favours several") and witty repartee that pass between the play's wooing characters. We follow downstream signaling events, describing the action of a MAP kinase cascade, and the activation of the Ste12 transcription factor; we track, in parallel, the advancement of the characters' "love-feat." We see, finally, how resultant changes in gene expression lead to cell fusion, creating a/alpha offspring. We conclude with a survey of pheromone function in other organisms, particularly insects, and describe roles in non-reproductive signaling, including foraging and predator detection.

30) Circadian Clocks, *As You Like It*

In *As You Like It*, Rosalind proposes a mechanism that may underlie time perception. According to her theory, rhythmic oscillations—"sighing every minute and groaning every hour"—create an internal record, functioning "as well as a clock." Rosalind in addition identifies sub-classes in which this mechanism may function imperfectly. For "a thief to the gallows" time passes abnormally quickly; for "lawyers in the vacation," it does not appear to pass at all. In this lecture, we examine molecular mechanisms underlying the function of the circadian clock. We sketch a range of negative feedback loops, noting examples that operate at the level of transcription, translation, and protein function. We discuss the physiological importance of the clock, enabling the organism to alter its behavior in anticipation of challenges associated with particular times of the day. In this framework, we also discuss the functions of genes that are downstream of the clock, whose expression is similarly cyclic. We look at the persistence of the clock, with reduced accuracy, in the absence of external cues; we look, also, at ways in which the clock may be reset, as triggered by light. We conclude by examining the behavior of mutants in which the clock machinery is abnormal, comparing them with Rosalind's catalogue of "diverse persons," who measure time in "diverse paces."

31) Telomeres and Cellular Senescence, *The Second Part of King Henry the Fourth*

In *The Second Part of King Henry the Fourth*, the "withered" Falstaff is compared to a candle, "the better part burnt out." In this lecture, we examine similarities between candles and chromosomes, each of which shorten as they age. We look in greater detail at the mechanism of DNA replication, first introduced in Lecture 20. We reexamine the DNA monomer, emphasizing its 5' and 3' carbons, and observe that this polarity is also retained in the polymer. We discuss the action of DNA polymerase, as aided by DNA primase, and compare the progress of replication on the leading and lagging strands. We see also that the rules governing DNA polymerase lead to a reduction of chromosome length each replication cycle. In this context, we reintroduce the telomere, characterizing it as a kind of buffer. We speculate on the relative telomere lengths of chromosomes derived from characters in the play; we in particular compare those of the young prince with those of the dying king. We sketch the action of telomerase, describing the role of

its RNA and protein parts; we in addition see how telomerase enables some cells, particularly gametes, to "keep no tell-tale to his memory that may repeat and history his loss to new remembrance." We trace, finally, additional "characters of age" related to telomere loss, including the failure to proliferate, as evaluated in cell culture. We conclude by reflecting that telomeres may serve as a kind of doomsday calendar, of the sort ascertained by the dying king: "...even there my life must end. It hath been prophesied to me many years."

32) Apoptosis, *Antony and Cleopatra*

In *Antony and Cleopatra*, multiple characters kill themselves, some with swords and others with poisonous snakes. Two main inputs prompt these suicides. The first is the fear of shame; the second is grief. In this lecture, we examine cell suicide, as mediated by proteases. We outline the importance of apoptosis, characterizing its roles both in normal development and in response to damage. We look at two apoptotic pathways, the extrinsic and intrinsic. We look, in the first instance, at the role of the death receptor, and, in the second, at the role of cytochrome *c* release by the mitochondria. We examine the caspases in greater detail, dividing them into initiator and effector classes, and describe their activation through cleavage. We trace, finally, the disassembly of the apoptotic cell, and its consumption by macrophages.

33) Cancer, *The Second Part of King Henry the Sixth*

In this lecture, we use *The Second Part of King Henry the Sixth* to trace the genesis of malignant growths. We compare the kingdom, composed of subjects, to an organism, composed of cells. In this framework, we discuss the importance of selfless behavior ("for the public good"). We see that, just as a kingdom functions most efficiently in the absence of rebellion ("loyal, true and crimeless"), the body also functions best when its cells are constrained by strict rules. We review the cell cycle, tracking progress through the G1, S, G2, and M phases, and discuss the functions of the cyclins and Cdk. We compare the role of Gloucester, "Lord Protector," to that of a tumor suppressor, and see that, just as his murder de-constrains rebellious activity, the inactivation of a tumor suppressor de-constrains cellular proliferation. We in contrast characterize military regiments as oncogenes: normally, they operate to maintain order but, when altered by activating mutations, they serve destructive purposes. We examine the aberrant behavior of cancer cells ("we [are] in order when we are most out of order"), paralleling it with the bizarre anarchism of Cade's supporters ("kill all the lawyers") and the "bedlam and ambitious humour" that animates York's faction. We look also at unfair tricks employed by tumors, including the excretion of factors that promote their own growth, which we compare to Cade's untraditional self-empowerment through self-knighting ("To equal him, I will make myself a knight presently"). We conclude by surveying a range of cancer types, and discuss the difficulty of devising treatments that are both effective and cancer cell specific.

34) Antigen Presentation, *The Third Part of King Henry the Sixth*

In *The Third Part of King Henry the Sixth*, severed heads, mounted on the town gates, are used to communicate information about the town's interior. Evidencing the defeat of noteworthy men, these heads demonstrate the town's allegiances. York's head, processed and displayed, indicates control by Queen Margaret. Later, Clifford's head, similarly presented, indicates control by Edward IV. In this lecture, we compare the practice of mounting heads to town gates to the practice of mounting protein fragments onto cellular MHC receptors. We contextualize this comparison by introducing basic themes in adaptive immunity. We define pathogens and antigens, and sketch the functions of the B-cells and T-cells. We examine the course of a viral infection, tracking the virus' uptake by a cell, and its subversion of cellular machinery to produce viral proteins. We look at the processing of viral proteins by the proteasome—comparing it to the decapitations of York and Clifford—and their ER-mediated export to the cell exterior, complexed with the MHC. We see how, thus presented, the protein fragments serve as a molecular confession, evidencing events on the interior. We conclude by examining strategies employed by some viruses to avoid detection, including interference with the MHC.

35) Autoimmune Disease, *Julius Caesar*

In *Julius Caesar*, an angry mob attacks Cinna the Poet after mistaking him for Cinna the Conspirator ("Tear him, tear him!"). In this lecture, we examine how similar errors, occurring at the cellular level, can cause the immune system to target innocuous "self" tissue, leading to disease. We chart the maturation of T cells in the thymus, and describe the construction of the T cell receptor via V(D)J recombination. We trace the stringent selection that follows the acquisition of this receptor, emphasizing mechanisms that normally eliminate autoreactive cells. More briefly, we consider parallel events occurring during the maturation of B cells. We in addition trace the activities of T-cells following their exit from the thymus and look at additional mechanisms that normally prevent the attack of self tissue. We discuss, finally, at what happens when these protective mechanisms fail. We follow the disease course of lupus, type 1 diabetes, and multiple sclerosis. At the same time, we continue to draw parallels with political events in the play, including Caesar's betrayal by men he trusted ("Et tu, Brute?"), and the destructive civil war that follows. We conclude with a discussion of available therapies, including immunosuppressive drugs, and describe the importance of mouse research models.

36) Protein Purification, *The Life of King Henry the Fifth*

In *The Life of King Henry the Fifth*, the king attempts to remove the familial guilt of Richard's murder. He employs a precise protocol, containing specific quantities: "five hundred poor"/"twice a-day"/"two chantries." In this lecture, we discuss the use of protocols in the biological laboratory, similarly aimed at removing impurities. We review the mixture of materials present in a biological cell—proteins, lipids, nucleic acids, carbohydrates, etc.—and see how each adds to the difficulty of isolating pure samples. We survey a range of protocols used for protein isolation; we also look at techniques for protein analysis, including Western blot and mass spectrometry. We focus in particular on the utility of protein tagging, which we compare to the strategy employed

Williams and the king, each wearing a conspicuous "gage" ("my glove in his cap"), in order that they might identify one another after the battle. We look, finally, at calculations of yield and loss, which we contextualize in terms of the king's own efforts to quantify the number of French soldiers killed, as compared to the number of English lost, during his war in France.

37) Gene Insertion, *Two Gentlemen of Verona*

In *Two Gentlemen of Verona*, Silvia directs Valentine to compose a letter. Valentine, driven by a "duty to your ladyship," obediently composes it. Despite obvious clues, he is incapable of perceiving Silvia's joke ("she hath made you write to yourself"). Obtuse, yet "very clerkly," he insists that he will serve her again, "a thousand times as much." In this lecture, we compare Silvia to a molecular biologist and Valentine to a laboratory organism. We see how biologists, exerting comparable control, can direct organisms to "write" new gene products. We survey protocols for the insertion of foreign genes, as employed in a range of laboratory models, and distinguish between methods for random and site-specific insertion. We focus on two applications: the production of human insulin by bacteria and the expression of GFP in mice. We note, in each instance, that the organism labors under a misimpression that is precisely the opposite of Valentine's: while believing that it is producing the protein for its own benefit, it is actually producing it for another's. We conclude by considering the problem of post-translational modification, and how this can complicate efforts to produce certain human proteins using non-human systems.

38) Plasmids, *All's Well that Ends Well*

In *All's Well That Ends* Well, rings serve important roles. They act as family heirlooms, indications of danger ("by this token I would relieve her"), and evidence of marriage consummation. Rings are also passed from person to person—either vertically, "from son to son," or horizontally, from the king to Helena to Bertram. In this lecture, we compare these macroscopic rings, composed of metal, to plasmid rings, composed of DNA. We look first at naturally occurring plasmids, highlighting their role in antibiotic resistance, and diagram a typical structure. We introduce bacterial conjugation as a natural mechanism of plasmid transfer, and compare it with the liaison between Helena and Bertram. We in addition consider the co-option of plasmids to serve in research, focusing on their role in laboratory yeast. We survey, finally, a range of transformation protocols and discuss the use of drop-out media to facilitate plasmid selection.