

MM

Molecules to Medicine

Course Goals

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1. Explain how the normal human cell is constructed and how it functions.
2. Describe the basic principles of DNA structure, synthesis and repair.
3. Describe RNA structure, major types of RNA and their function, synthesis of mRNA, and mechanisms of gene regulation.
4. Discuss amino acids, protein primary, secondary, tertiary, and quaternary structure, and principles of translation and translational control, and basic principles of enzyme function and kinetics, and mechanisms of protein degradation.
5. Comprehend the basic principles of human inheritance, the molecular basis of inherited disease, and methods to search for human disease genes.
6. Comprehend the basic principles of imprinting, cytogenetics, preparing and interpreting a pedigree, genetic regulation of sex determination, and describe the major forms of inherited disease encountered clinically.
7. Describe and discuss the major structural compartments, organelles, and cytoskeletal components in the cell and their function.
8. Explain the basic principles of intracellular trafficking, and intracellular signaling.
9. Provide a basic understanding of membrane structure and function, and basic principles of cell physiology, including cell composition and volume regulation, membrane potential, gated channels, and action potentials.
10. Describe how the cells in the body form major types of functional tissue, including epithelium, connective tissue, and muscle, and describe normal histology of human tissues.
11. Describe the underlying molecular and cellular perturbations of certain human diseases and how these human diseases present clinically.
12. Understand the basic principles of bioenergetics that govern catabolic and metabolic reactions that occur within cells.
13. Understand basic techniques in molecular biology: PCR, restriction enzyme digestion of DNA, gel electrophoresis on nucleic acids and protein and their application for Southern & Northern blotting, Sanger, and NexGen genomic sequencing for the diagnosis of human disease.
14. Understand how the cell cycle is orchestrated and regulated through actions of specific cyclins, cyclin-dependent kinases, inhibitors of kinases, checkpoints, and how acquired or inherited alterations of cell cycle regulation lead to cancer.
15. Understand basic mechanism of programmed cell death, including apoptosis and autophagy.
16. Explain how human genetic variation relates to measured phenotypic variation in health, disease, and differential response to medications.
17. Understand and apply genetic counseling and related ethical practices in clinical genetic situations.

AY 2018-2019

Molecules to Medicine

Session Learning Objectives

Acids, Bases and Buffers (No Lecture; Panopto Only)

1. Describe the law of mass action.
2. Define pH and pKa.
3. Write the Henderson-Hasselbalch equation for any given weak acid or base.
4. Define the Henderson-Hasselbalch equation for the bicarbonate buffer system in extracellular fluid and use it to evaluate clinical lab data.
5. Define normal blood pH, $[\text{HCO}_3^-]$ and pCO_2 .
6. Describe how weak acids and bases work to buffer pH and define the pH range of maximal buffering capacity.
7. Use the Henderson-Hasselbalch equation to solve problems of how pH changes in defined buffers, i.e., determine how many equivalents of acid or base are needed to titrate the ionizable groups(s) of a weak acid or base from a starting pH to a final pH, given its concentration and pKa.

Action Potential I

1. Explain what an action potential is and understand that it is important for neural signaling.
2. Describe how the activation and inactivation gates of sodium channels are affected by changes in the membrane potential, and how the activation gates of potassium channels are also affected by changes in the membrane potential.
3. Describe how the action of voltage-gated sodium and potassium channels generates the action potential.
4. Explain the causes of the membrane's refractory period.
5. Explain the mechanism determining the threshold for action potential generation.
6. Explain how neurons accommodate to slow depolarization.

Action Potential II

1. Explain why action potentials are necessary for rapid communication over long distances.
2. Identify the "safety factor" for conduction, and explain how this supports AP conduction along branching axons, and enables the axon to generate action potentials at a higher rate.
3. Describe the role of refractoriness in preventing action potentials from reversing direction, and propagating "backwards".
4. Explain how action potential diameter affects conduction velocity.
5. Explain how myelin sheathing supports AP conduction.

Alzheimer Vignette

1. Comprehend the pathophysiology of Alzheimer's Disease.
2. Describe the central role of post-translational amyloid precursor protein processing in the pathogenesis of Alzheimer's Disease.
3. Consider interventions that might help delay onset or prevent the development of Alzheimer's Disease.

Amino Acids, Peptides and Proteins I

1. Identify the α carbon, the NH_2 , COOH , and side chains (R groups) of an amino acid and distinguish between hydrophobic, polar, acidic and basic side chains.
2. Describe the function of disulfide bonds within proteins.
3. Describe the major post-translational modifications (PTM) of amino acid side chains in proteins and understand the basic mechanism of PTM-related disease/medicine.
4. Understand that the amino acid sequence determines protein function; mutations in amino acid sequence can cause genetic disease.
5. Recognize that proteases and the specific breaking of peptide bonds can have important functions.
6. Describe secondary, tertiary, and quaternary protein structure and delineate the contribution of covalent and non-covalent bonds to protein structure and function.
7. Understand how to use K_d to quantify binding affinity; Explain how binding specificity can be achieved.
8. Explain why hemoglobin is a good oxygen transporter. Explain the molecular basis of carbon monoxide poisoning.
9. Define the general function of chaperones. Explain why sometimes protein disulfide isomerase or protein prolyl isomerases are required for protein folding.
10. Recognize that that protein misfolding is the major cause of prion disease, Alzheimer's disease, and Parkinson's disease; Identify the secondary structure changes and the infectious agent in prion disease.

Amino Acids, Peptides and Proteins II

1. Describe hydrogen bonds and their role in secondary structure formation.
2. Describe the two most common protein secondary structures.
3. Explain tertiary and quaternary structures.
4. Explain the role of loops in protein structure and function.
5. Explain how to use K_d to represent binding strength.
6. Explain how binding specificity can be achieved.
7. Explain how heme enables myoglobin to bind oxygen.
8. Explain the molecular basis of carbon monoxide poisoning.
9. Explain why hemoglobin is a good oxygen transporter.

Androgen Receptors Clinical Vignette

1. Identify the sources of androgen in the body relevant to prostate cancer.
2. Describe the structure and function of the androgen receptor in prostate cancer.
3. Describe the mechanisms of resistance to traditional endocrine therapy for prostate cancer, describing the effects of enzalutamide and abiraterone on these mechanisms.

Apoptosis

1. Describe characteristic plasma membrane, cytoplasmic, and nuclear events of apoptosis.
2. Compare and contrast apoptosis and necrosis in terms of morphology, typical triggers of the two phenomena, and relative importance in physiological and pathological processes.
3. Name tissues in which there is most and least apoptosis. Suggest reasons for this difference.
4. Describe the role of caspases in apoptosis, and discuss the role that the mitochondrion may play in the process. Identify the roles of Caspases 8, 9, and 3.
5. Distinguish between the signaling of the intrinsic and extrinsic apoptosis pathways.
6. Discuss the essential biological difference between phagocytosis of apoptotic and necrotic cells.
7. Discuss the importance of apoptosis in tumor formation and progression.
8. Describe a mechanism by which one cell can induce apoptosis in another cell, and give an example.

Autophagy

1. Differentiate between two main types of autophagy: macroautophagy and chaperone-mediated autophagy.
2. Describe the process of macroautophagy.
3. Describe the rationale behind autophagy's protective action against neurodegeneration.
4. Identify mechanisms by which apoptosis induction and autophagy are connected.

Autosomal Dominant Disorders

1. Recognize and explain the characteristic patterns in a pedigree showing autosomal dominant inheritance.
2. Describe features that may complicate the assessment of an autosomal dominant pedigree.
3. Recognize and explain important concepts in dominant inheritance including penetrance, expressivity, locus heterogeneity and paternal age effect.
4. Recognize and describe the clinical features and molecular basis of Achondroplasia, Neurofibromatosis Type 1, Osteogenesis Imperfecta and Tuberous Sclerosis.
5. Describe the clinical features and unique mechanisms of Trinucleotide and Tetranucleotide Repeat disorders.
6. Recognize and describe clinical features and the molecular basis of Huntington Disease.

Autosomal Recessive Disorders

1. Describe common inheritance patterns of autosomal recessive disorders.
2. Calculate allele and carrier frequencies of a given autosomal recessive disease when provided with the disease frequency, and vice versa.
3. Know the clinical presentations, biochemical defects, genetic causes, diagnostic/screening tools and treatment if available for the three AR disorders discussed in class: Phenylketonuria, alpha 1-Antitrypsin Deficiency and Tay-Sach Disease.

Calcium Signaling

1. Describe the functions of cytoplasmic Ca^{2+} ion buffers and how these buffers affect cytoplasmic Ca^{2+} signals.
2. Describe the routes by which extracellular Ca^{2+} enters the cytoplasm, the routes by which Ca^{2+} moves out of the ER/SR into the cytoplasm, and the routes by which Ca^{2+} is extruded from the cytoplasm (a) into the extracellular space and (b) into the lumen of the ER/SR.
3. Describe EF hands and C2 domains, identify the archetypical protein that contains EF hands and the archetypical protein that contains a C2 domain, and determine whether these domains are present in other proteins.

Case Studies in Genetics

1. Explain and contrast the molecular genetic features and mechanisms of the following genetic diseases: Achondroplasia, Nonsyndromic deafness, Fragile X syndrome, Marfan syndrome, Rett syndrome, and Xeroderma Pigmentosum.
2. Recognize clinical signs and symptoms of Achondroplasia, Nonsyndromic deafness, Fragile X syndrome, Marfan syndrome, Rett syndrome, and Xeroderma Pigmentosum.
3. Correctly recommend and interpret genetic testing for Achondroplasia, Nonsyndromic deafness, Fragile X syndrome, and Marfan syndrome, Rett syndrome, and Xeroderma Pigmentosum.
4. Discuss the diagnostic approaches and ethical implications of the following two scenarios: 1) the use of genetic testing for couples at risk for a deaf child to reduce the risk of them having a child with congenital deafness, and 2) two deaf parents that use testing to ensure they have a child who is also deaf.

Cell Composition and Volume Regulation

1. Recite typical values for the volumes of extracellular fluid (ECF; about 14 liters; 1/3 of total body fluid), intracellular fluid (ICF; about 28 liters; 2/3 total body fluid), and plasma (2.8 liters, 20% of ECF) compartments.
2. Describe the major differences in ionic composition between ECF and ICF.
3. Describe the two most important functional properties of membranes, one conveyed by lipids, the other by channels and transporters.
4. Determine which direction an uncharged substance will move across a membrane, given its concentrations on the two sides.
5. Determine under a given set of conditions, whether a cell will swell or shrink and list the three mechanisms that different cells have evolved to keep from swelling and bursting.
6. Compare and contrast diffusion and osmosis.
7. Describe the effect of having a membrane with different, non-zero permeabilities (i.e., reflection coefficients less than 1) to different solutes.
8. Define molarity, osmolarity, equivalents, and tonicity, and describe how they are related to each other.

Cell Signaling

1. Describe principle types of detectors of extracellular signaling molecules.
2. List other "tools" of signaling pathways, including at least three 2nd messengers.
3. Describe at least three mechanisms for signal termination (including phosphodiesterases).
4. Evaluate a "pathway" for amplification and termination.
5. Identify "nodes" (such as calcium) and "modules" in a signaling pathway, and evaluate the potential for crosstalk in signal transduction.

Chromosomal Abnormalities

1. Describe the events in meiosis that produce genetic variability among offspring.
2. Compare and contrast mitotic and meiotic cell divisions.
3. Define and interpret the karyotypic nomenclature and designations used in cytogenetic reports to describe numerical abnormalities.
4. Describe the clinical features of the common human trisomies: 21, 18, and 13.

Chromosomal Rearrangements, Microdeletions and Microduplications

1. Describe the mechanism(s) of common chromosomal structural rearrangements.
2. Explain the difference between balanced and unbalanced structural rearrangements.
3. Assess the risks in families that are carriers of balanced translocations to have unbalanced progeny.
4. Identify and describe the clinical features of the most common contiguous gene syndrome in humans (this will be discussed again in the Molecular Cytogenetics lecture).

Cilia

1. Identify the components of cilia.
2. Explain how cilia are assembled.
3. Explain the differences between motile and sensory cilia.
4. Identify signaling pathways that function through cilia and explain why cilia are used for signaling.
5. Provide specific examples of how cilia function in development and tissue homeostasis.
6. Recognize the clinical features and cilia defects associated with ciliopathies.

Connective Tissues I

1. Describe the structural relationships among connective tissue and epithelia, blood vessels, and muscles.
2. Describe connective tissue cellular and extracellular components and their functions: State the types, origins, and functions of the different cell types found within connective tissues. Describe the components of the extracellular matrix, their functions, and how they are organized in different connective tissues.
3. For the proteins that form extracellular fibers, describe their types, their properties, and how they are made and assembled in the extracellular matrix.
4. Describe the basis and functional consequences of connective tissue diversity.
5. Describe how connective tissues are regulated upon tissue injury. Describe the events that occur following wounding and inflammation.

Connective Tissues II

1. For cartilage, describe its cellular and extracellular composition, its structural properties, and how it is organized. State the functions of cartilage tissue.
2. Describe how cartilage grows during fetal and child development.
3. State the characteristics that distinguish the three basic types of cartilage.
4. State the different cell types found in bone. For each cell type, describe their functions, their origins, and describe how they are organized in bone tissue.
5. Describe the composition of bone extracellular matrix, and the functions of the different components discussed in class and lecture notes. Describe where these extracellular matrix components are made, and how they are deposited to form bone matrix.

Connective Tissues III

1. Describe the two different processes that lead to bone formation. Describe how long bones grow in length and in width.
2. Describe the sequence of events that occur in bone remodeling.
3. Describe how bone formation and remodeling is regulated.
4. Describe how defects in bone remodeling leads to disease.
5. Describe how calcium is deposited and resorbed from bone matrix, and how regulation of bone cells controls the levels of blood calcium.

Control of Gene Expression I

1. Discuss the basics of eukaryotic transcription (DNA control elements, transcription factors) and the role they play in human disease.
2. Describe how diseases may arise from either a mutation in a DNA control element or a mutation in the DNA encoding a sequence specific DNA binding protein.
3. List major classes of activators and repressors and describe how their domains determine their role in combinatorial control of gene expression.

Control of Gene Expression II

1. Describe how chromatin structure affects transcriptional control and list the classes of chromatin remodeling factors and briefly describe their mechanism of action.
2. Describe how diseases may arise from dysfunctional chromatin remodeling.
3. Understand how chromatin modifiers are being targeted clinically and how this effects gene regulation.

Control of Gene Expression III

1. Describe how sequence specific DNA binding proteins are themselves regulated, and how their dysregulation may lead to human disease and list at least four mechanisms by which sequence specific DNA binding proteins are regulated..
2. Describe how the activity of nuclear hormone receptors is controlled, and how tamoxifen acts in breast cancer therapy.
3. Describe transcriptional heterogeneity and understand how it influences therapeutic outcome.

Crohn's Disease Vignette

1. Employ listening and empathy in actively listening to patients' symptoms and not dismissing them as "stress-related".
2. Appreciate why patients with inflammatory bowel disease experience feelings of shame and embarrassment related to their symptoms and their disease.
3. Describe how the activation of inflammatory bowel disease during puberty can impact patients' emotional and social development.
4. Formulate a medical history of inflammatory bowel disease patients that extends beyond merely asking them about frequency and quality of their bowel movements.
5. Organize a discussion about proceeding with an ostomy surgery for a patient with inflammatory bowel disease that incorporates the patient's own perspective and values in the patient-physician conversation.
6. Correctly diagnose clinical presentations of inflammatory disease.

Cystic Fibrosis Vignette

1. Describe the genetics, clinical features, and underlying protein defect in Cystic Fibrosis.
2. Describe current understanding of the pathophysiology underlying cystic fibrosis lung disease.
3. Describe the diagnostic and therapeutic approaches in cystic fibrosis.

Cytoskeleton I

1. Discuss and describe the concept of a cytoskeleton.
2. Describe microtubules and intermediate filaments of the cytoskeleton (their properties, their functional roles, and their protein composition).
3. Explain cytoskeletal dynamics and the role of certain proteins and drugs in tubulin polymerization/depolymerization.
4. Explain the concept of molecular motors and summarize the mechanisms of tubulin-based movement and intracellular transport.
5. Explain the role of microtubules in mitosis.
6. Analyze the cytoskeleton in the context of disease processes.

Cytoskeleton II: Actin & Cell Motility

1. Describe the three types of cytoskeletal elements, their properties, their functional roles, and their protein composition.
2. Discuss cytoskeletal dynamics and the role of certain proteins in actin filament formation, polymerization/depolymerization.
3. Describe the role of the actin cytoskeleton in epithelial cell polarity and summarize some diseases caused by disruption of the actin cytoskeleton and normal cell polarity.
4. Explain the concept of molecular motion, and the mechanism of actin-based organelle movement and muscle contraction.
5. Discuss the concept and the key steps of cell movement.
6. Discuss cell motility in the context of developmental and disease processes.
7. Describe the role of actomyosin ring in cell division.
8. Describe the mechanisms regulating the establishment and activation of the actomyosin ring and identify examples of asymmetric cell division.

DKA Vignette

1. Identify straightforward diabetic ketoacidosis (DKA).
2. Describe the major metabolic disturbances in DKA.
3. Describe the stimulus for insulin release and describe three target site actions of insulin.
4. Discuss the risk for cerebral edema in DKA.

DNA I & II

1. Distinguish purines and pyrimidine bases, ribose and deoxyribose, ribo- and deoxyribo- nucleosides, nucleotides, nucleoside di- and tri- phosphates.
2. Discuss the relative solubility of DNA components in the context of gout and Lesch-Nyan disease.
3. Identify the basic chemistry of the phosphodiester bonding in nucleotide polymers, polymerization, and the structural and functional implications of hydrogen bonding.
4. Explain the chemistry of DNA polymerization and how nucleoside analogues are used as drugs.
5. Explain chemical modifications of bases in DNA and their significance to disease and disease treatment.

DNA Repair

1. Describe the sources and nature of damage to DNA, examples of heritable and non-heritable diseases caused by defective DNA repair pathways.
2. Compare and contrast mechanism and function of base excision repair, mismatch repair, nucleotide excision repair, and double strand break repair with particular regard to the type of DNA lesion corrected.
3. Explain the rationale of poly (ADP-ribose) polymerase inhibitors and DNA damage response modulators in cancer therapy.

DNA Replication

1. Draw a mammalian DNA replication fork with all relevant enzymes, their order of operation, and indicate the appropriate directionality of each strand.
2. Discuss the function and activity of telomerase.
3. Give examples of human diseases caused by DNA replication defects and use of drugs that target DNA replication machinery.

Double-strand (DS) DNA Break Repair

1. Name five sources of DNA double-strand breaks.
2. Distinguish between the two mechanisms used to repair DNA double-stranded breaks and explain why defects in either of these two modes of double-strand break repair can increase cancer risk.
3. Give three examples of diseases directly linked to defective double strand break repair.

Down Syndrome Vignette

1. Describe the chromosomal abnormalities associated with Down Syndrome and how to test for them.
2. Describe the physical features (Phenotype) seen in a patient with Down Syndrome.
3. Recognize the medical problems seen in patients with Down Syndrome.
4. Describe the developmental and behavioral phenotype of a patient with Down Syndrome.

EBM Small Group (Required): Using Medical Literature for Patient Care

1. Evaluate a cohort study. Apply concepts that relate to validity of cohort studies, including selection bias, selection of comparison group, exposure measurement, confounding, and loss to follow-up. Explain its relevance to patient care and clinical decision-making.
2. Define criteria for inferring causality from statistical associations including Hill criteria and apply to an example.
3. Explain the difference between statistical significance and clinical significance. Understand p-values and confidence intervals. Accurately interpret p-values and confidence intervals in a clinical context.
4. Recognize statistical methods commonly used in the medical literature, including t-tests and chi-square tests, correlation, ANOVA, logistic regression, linear regression, survival analysis/Cox proportional hazards model, Kaplan-Meier curve, forest plot. Understand how to interpret their results.
5. Evaluate a study about therapy. Apply concepts that relate to validity of RCTs including randomization, concealed allocation, intention-to-treat, blinding, significance, and power. Explain its relevance to patient care and clinical decision-making.
6. Calculate number needed to treat/harm (NNT/H). Explain how it can be used to communicate risk to patients.
7. Describe barriers to understanding evidence and explain appropriate techniques for communicating numeric and other information to colleagues and patients.

EBM: Applying Clinical Trial Results

1. Critically appraise an RCT.
2. Explain the difference between statistical significance and clinical significance.
3. Calculate and apply risk ratios and absolute risk. Explain the circumstances in which they are appropriate to use and how they are interpreted.
4. Calculate number needed to treat/harm (NNT/H), absolute risk reduction and relative risk reduction. Differentiate between disease-oriented outcomes and patient-oriented outcomes.
5. Describe barriers to understanding evidence and explain appropriate techniques for communicating numeric and other information to patients.
6. Identify and use summary sources, practice guidelines, pre-appraised sources, and sources of individual studies.

EBM: Best Evidence = Systematic Reviews

1. Distinguish between narrative review articles, systematic reviews, and meta-analysis and understand issues in using them such as publication bias, forest plots, and heterogeneity.
2. Evaluate a meta-analysis and apply concepts that relate to its validity, including asking a focused clinical question, specifying inclusion criteria, comprehensiveness of literature search, quality assessment of included studies, and assessment of heterogeneity. Explain its relevance to patient care and clinical decision-making.

EBM: Finding Disease 1

1. Describe characteristics of a screening test.
2. Calculate and apply common diagnostic/ screening test information including sensitivity, specificity and predictive values.

EBM: Finding Disease 2

1. Describe characteristics of cross-sectional studies, explain how these characteristics may result in bias, and recognize appropriate methods for minimizing these biases.
2. Discuss the strengths and limitations of cross-sectional studies and the clinical questions best answered by this study type.
3. Explain the difference between risk and odds. Calculate an odds ratio. Explain the circumstances in which each is appropriate to use and how each is interpreted.
4. Calculate and apply common diagnostic/screening test information including sensitivity, specificity, and predictive values. Describe how predictive values are influenced by disease prevalence.
5. Explain appropriate techniques for communicating numeric and other information from screening and diagnostic studies to colleagues and patients.

EBM: Interpreting Clinical Trials 1

1. Understand the difference between random error and bias and how these can be minimized. Define validity.
2. Describe characteristics of randomized controlled trials (RCTs) such as randomization, blinding, allocation concealment, intention-to-treat analysis (as compared with per-protocol or as-treated analyses), and follow up, and explain how these characteristics reduce bias.
3. Explain the circumstances in which it is appropriate to use risk ratios and how they are interpreted.
4. Understand type 1 and type II errors, null hypotheses, alpha level, power, p-values and confidence intervals. Accurately interpret p-values and confidence intervals in a clinical context.

EBM: Interpreting Clinical Trials 2

1. Evaluate a study about therapy. Apply concepts that relate to validity of RCTs including randomization, concealed allocation, intention-to-treat, and blinding.

EBM: Interpreting Observational Studies

1. Define epidemiologic concepts of incidence, mortality, case fatality and prevalence.
2. Recognize differences in study design for cohort studies and randomized controlled trials. Discuss the strengths and limitations of each and the clinical questions best answered by each study type.
3. Define criteria for inferring causality from statistical associations and apply to an example.
4. Describe characteristics of cohort studies, explain how these characteristics may result in bias, and recognize appropriate methods for minimizing these biases. Critically appraise cohort study.

EBM: Interpreting Statistics

1. Define statistical measures commonly used in the medical literature, including sampling, normal distribution, mean, median, mode, variance, standard deviation, and range.
2. Recognize statistical methods commonly used in the medical literature, including t-test, Chi-square test, Correlation, Multivariate analysis, ANOVA, linear regression, logistic regression, survival analysis, Kaplan-Meier curve, Cox proportional hazards model. Understand how to interpret their results.

EBM: Observational Study Basics

1. Recognize differences in study design for both observational and experimental studies.
2. Explain how characteristics of observational studies may result in bias.

Endocytosis and Protein Degradation

1. Describe two major routes for small volume endocytosis and discuss how endocytic pathways are related to viral infections and to bacterial ingestion by macrophages.
2. Explain how quality control of protein synthesis ensured by the ER.
3. Describe two types of molecular chaperones.
4. Describe the proteasome and the role of ubiquitin in protein degradation.
5. Describe the functions of the lysosome and discuss storage diseases that occur due to dysregulated lysosomal protein metabolism.

Enzyme Kinetics I & II

1. Describe what enzymes are, the characteristics of enzymes, and thermodynamically how they increase the rate of a reaction. Define the terms: catalyst, activation energy, free energy of the reaction.
2. Describe how enzymes work using the terms: binding of the transition state, induced fit, covalent chemistry, metal ion chemistry, and general acid-base chemistry.
3. Define the terms cofactor and coenzyme.
4. Describe the significance of the terms K_m and K_{cat} (know what it means if one enzyme has a lower or high K_m than another, etc.) and estimate the value of K_m from a graph of reaction velocity versus $[S]$.
5. Describe four different types of inhibitors and, in general, how each works (competitive, uncompetitive, mixed, and irreversible).
6. Describe four types of enzyme regulation mechanisms and, in general, how each functions (allosteric, covalent modification, binding of another protein, proteolytic cleavage).

Epigenetics

1. Describe the four main characteristics of epigenetic phenomena.
2. Explain the basic principle of Waddington's epigenetic landscape.
3. Describe and explain three specific examples of epigenetic phenomena.
4. Describe how DNA methylation can be inherited through cell division.
5. Describe and explain three chemical modifications to DNA or histones that can potentially be inherited.
6. Describe and explain how epigenetic mechanisms and inheritance can occur both inside and outside the nucleus.
7. Describe a specific type of gene that, when aberrantly methylated with 5meC, can lead to cancer and an approach to therapeutic intervention in this case.

Epithelia I

1. State the structural arrangements, classifications, and functions of epithelial tissues, and state their general structural relationships (orientation) to connective tissue, blood vessels, muscle, and neurons (peripheral nervous tissue).
2. Describe the epithelial to mesenchymal transition during development.
3. Describe the cellular basis for apical-basal polarity of epithelial cells and describe the functions of epithelial polarity.
4. State the different cell junctions that connect epithelial cells to one another and to the basal lamina, and describe their key components and functions.

Epithelia II

1. State the types and functions of the different cell surface modifications on epithelial cells.
2. Describe basal laminae by stating their basic components, their functions, the basis of their diversity, and their structural relationship to epithelia and other tissues.
3. Compare and contrast exocrine and endocrine glands in terms of their development, general structure, and functions. For both types of glands, trace the path that a secreted molecule must take from its synthesis to its destination, and describe all the barriers/structures the molecule must cross en route.

Epithelia III

1. Describe how epithelial tissues are maintained and regulated, and describe the properties, functions, regulation and development of epithelial stem cells.
2. State the general terms for epithelial-derived cancer, and describe how defects in epithelial cell regulation can contribute to cancer.
3. Describe how tissue sections are made and visualized for histological (microscope) examination, both for general staining and for specific staining of specific proteins and RNAs. Distinguish what general stains visualize from what immunostaining or nucleic acid-staining techniques visualize. NOTE: Information on this objective is presented in the Intro-Epithelia Histo PDF (Histology lab material), and will also be presented in class.

Epithelial Transport

1. Explain the difference between the apical (a.k.a. mucosal / luminal) vs. basolateral (a.k.a. serosal / peritubular) surface of the membrane.
2. Explain how pericellular transport works, and how it compares to transcellular transport.
3. Explain the mechanisms generating the driving force behind the transport.
4. Explain how nutrients are absorbed by the GI tract.
5. Explain how water absorption occurs.

Extracellular Matrix & Cell Adhesion

1. Discuss the contributions of the extracellular matrix to cell and tissue function.
2. Define the four major classes of extracellular matrix components and their properties.
3. Define two types of fibrillar proteins and at least two types of multidomain adapter proteins of the extracellular matrix.
4. Discuss the role of matrix metalloproteinases in extracellular matrix remodeling.
5. Discuss the role of adhesion in cell function and survival.
6. Define and describe at least three different types of cell adhesion molecules and their ligands.
7. Discuss the role of cell adhesion molecules in signaling.
8. Describe proteins associated intracellularly with cell adhesion molecules.
9. Discuss the extracellular matrix and cell adhesion in the context of disease processes.

Finding Disease Genes

1. Describe the rationale and approaches for finding disease genes.
2. Explain the differences between genetic association studies (candidate gene and genome-wide), genetic linkage studies, and exome/genome sequencing studies.
3. Recognize the strengths, weaknesses, and typical (and optimal) applications of genetic association, genetic linkage, and exome/genome sequencing studies.
4. Describe the basic statistical approaches used to test for genetic association and to test for genetic linkage.
5. Recall the three most commonly used types of DNA polymorphisms used as tools for finding genes.
6. Discuss the advantages and limitations of the emerging use of genome/exome sequencing in genetic analysis and genetic testing.

Gates and Channels

1. Describe the basic structure of Nav and Kv ion channels (number of subunits or repeats, number of membrane-crossing alpha helices per repeat/subunit) and whether this pattern is common to all known ion channels.
2. Describe the basic principles of channel selectivity, the features of ions that are important for selectivity, and the role of dehydration of the ions.
3. Describe specific structures of Nav and Kv channels that serve as the voltage sensors, the selectivity filter, and the activation/inactivation gates and describe where these gates are located with respect to the membrane orientation of Nav and Kv.
4. Describe what structural features of Nav and Kv lead to "sidedness" of agents that act on these channels and to "state-dependence" of action.

Genetic Counseling

1. Recognize the factors that have impacted the process of genetic counseling and how it is currently practiced.
2. Identify present day goals of genetic counseling.
3. Recognize indications for genetic counseling.
4. Identify fundamental ethical principles of genetic counseling as it is practiced today.
5. Recognize the reproductive options currently available for couples with increased risk for having a child with a genetic disorder, including which options are appropriate or available given the mode of inheritance and/or diagnostic information available.
6. Recognize factors that may impact a client's perception of risk and their selected course of action.

Genetic Disorders of Sexual Development

1. Describe the genetic mechanisms and clinical characteristics of disorders of sex chromosomes.
2. Explain the genetic regulation of sexual differentiation.
3. Describe the basic embryology of dimorphic human reproductive organs.
4. Describe the clinical approach to the diagnosis and management of disorders of sexual differentiation.
5. Discuss and appreciate the sensitivity of concept of gender identify in patients with Differences of Sexual Development.

Genetic Testing

1. Define what broadly or narrowly constitutes a "genetic test."
2. Describe the basic approaches, advantages, limitations, and interpretations of different types of genetic tests.
3. Interpret genetic testing results and distinguish between "informative" and "non-informative" results.
4. Explain how allelic heterogeneity and genetic heterogeneity can affect the performance and interpretation of genetic tests.
5. Discuss the ethical and legal issues related to the confidentiality of genetic test results.

Genome Editing

1. Describe and distinguish between the following three genome-editing systems: Zinc Finger Nucleases (ZFNs), Transcription Activator-Like Effector Nucleases (TALENs), and Clustered Regularly-Interspaced Short Palindromic Repeats (CRISPR)/Cas9.
2. Identify the key components of the bacterial CRISPR/Cas9 system and describe how this system provides bacteria immunity from viral infection.
3. Discuss the similarities and differences between the two main methods of DNA repair that occur after genome editing: Nonhomologous End Joining (NHEJ) and Homology Directed Repair (HDR).
4. Select and justify which genome editing strategy is most applicable (based on strengths and weaknesses) to various disease models as we shall practice in the classroom session.
5. Describe and distinguish between the following three genome-editing systems: Zinc Finger Nucleases (ZFNs), Transcription Activator-Like Effector Nucleases (TALENs), and Clustered Regularly-Interspaced Short Palindromic Repeats (CRISPR)/Cas9.

Genome Organization

1. Describe the fundamental principles regarding the evolution and organization of the human genome mentioned in the outline.
2. Explain why genome variation is an essential fuel of evolution and adaptation, but it also produces human disease.
3. Discuss the dynamic nature and non-random organization of the human genome as described in the outline.
4. Describe how frequently a single-nucleotide polymorphism (SNP) is likely to occur between two individuals.
5. Describe the types of genetic variations that occur between genomes.
6. Describe the following characteristics of the genome: a) gene-rich; b) gene-poor; c) stable; d) unstable; e) GC-rich; f) AT-rich; g) euchromatic; and h) heterochromatic.
7. Describe how in genome sequencing focused on euchromatic regions, there is no completely sequenced and assembled human genome.
8. Discuss and explain why many gaps still remain even in euchromatic regions.
9. Describe what categories genomic DNA sequences can be assigned to and the frequency of each class.
10. Describe the types, locations and frequency of repetitive DNAs that exist in the human genome.
11. Describe the estimated number and different types of human genes.
12. Discuss that genes often exist in gene families and explain how gene families arise by gene duplication.
13. Discuss the advantages of gene duplication as an evolutionary mechanism and the disadvantages of gene copy number changes in terms of causing diseases.
14. Describe what the limitations are of current genome sequencing and screening methods, and how this relates to the "missing heritability" problem.

Genomic Imprinting

1. Describe the concept and mechanisms of genomic imprinting and DNA methylation.
2. Identify which main chromosomes have imprinted regions.
3. Describe the clinical features of common genetic disorders associated with imprinting.
4. Recognize the pedigree inheritance patterns of imprinted disorders.

Histology Lab I & II

1. Describe how tissue sections are made and visualized for histological (microscope) examination, both for general staining and for staining with molecule-specific probes (antibodies and RNA probes). Distinguish what general stains visualize from what molecule-specific staining techniques visualize.
2. Identify and recognize cell nuclei in any tissue section, and identify material as within or outside of cells.
3. Recognize the internal spaces of big and small tubes and other tissue compartments, as well as the external edges of tissues when they are included in the section.
4. Compare and contrast the different cellular and extracellular elements within a given section to help recognize what is being seen.
5. Identify cells and structures of the basic tissues, and state their functions.

Introduction to EBM: Facts & Numbers for Patient Care

1. Explain the value of evidence over opinion in making medical decisions and in the practice of life-long learning.
2. Define evidence-based medicine (EBM). Explain the EBM cycle of asking clinical questions, using appropriate resources to select high quality evidence, and applying evidence to individual patients.
3. Describe the evidence hierarchy.

Introduction to Mendelian Inheritance

1. Explain and distinguish between Mendel's Laws of Inheritance.
2. Discuss how the following two principal factors determine the inheritance patterns seen in single-gene disorders: a) quality of the phenotype (dominant vs. recessive), and b) location of the gene locus (autosomal vs. sex chromosome).
3. Analyze a pedigree and recognize and distinguish between the major modes of Mendelian Inheritance, including autosomal dominant, autosomal recessive, X-linked dominant, and X-linked recessive.
4. Explain and compare various 'threats' to Mendelian inheritance patterns, particularly the threats due to variability in penetrance, expressivity, and pleiotropy.

Li-Fraumeni Vignette

1. Describe the criteria for classifying a hereditary cancer syndrome.
2. Describe the Knudson two hit hypothesis.
3. Describe how germline mutations in p53 lead to the development of Li-Fraumeni Syndrome.

Lung Cancer Vignette

1. Describe the molecular biology of lung cancer as it relates to treating lung cancer in the clinic.
2. Apply molecular targeted therapies to treat lung cancer.
3. Explain how to select patients in order to give the right treatment to the right patient ("Personalized medicine" or "Precision medicine").
4. Analyze the differences between prognostic and predictive biomarkers.
5. Describe the status of lung cancer screening.

M2M Required Small Groups - Bench to Bedside I: Gaucher

1. Explain the causes and risk factors of thrombocytopenia and how Gaucher disease leads to thrombocytopenia.
2. Explain causes and risk factors of hepatosplenomegaly and how Gaucher disease leads to hepatosplenomegaly.
3. Explain the underlying cause, genetic inheritance, and major pathophysiological features of Gaucher disease.
4. Describe major subtypes and clinical features of Gaucher disease, including physical and neurological signs, ocular motor and other manifestations.
5. Describe major cellular pathology and clinical manifestations of Gaucher disease.
6. Explain how to diagnose Gaucher disease and correctly analyze tests for Gaucher disease.
7. Explain the major steps in medical, surgical, and pharmacological management of Gaucher disease.
8. Describe limitations of current therapies for Gaucher disease, including cost; discuss ethical issues of ERT and identify the current unaddressed needs for Gaucher patients.

M2M Required Small Groups - Bench to Bedside II: Scientific Method

1. Describe the scientific method.
2. Discuss and provide examples of the key elements of the scientific method.
3. Evaluate how the scientific method applies to medical research and clinical medicine.
4. Apply the scientific method to clinical reasoning.

M2M Required Small Groups - Research Ethics

1. Identify the three core ethical principles relevant to clinical research.
2. Apply the core ethical principles to a case.
3. Describe the basic functions of an Institutional Review Board (IRB).

Membrane Fusion

1. Describe and understand the basic mechanisms of intracellular vesicle transport.
2. Describe and understand the basic regulation of intracellular vesicle transport.

Membrane Potential

1. Compare qualitatively the relative strengths of electric and osmotic forces.
2. Describe the two forces acting on an ion moving across a membrane.
3. Define and describe the difference between an equilibrium potential, reversal potential, and recorded membrane potential.
4. Recognize that each and every ion species has its own, independent equilibrium potential.
5. Understand the number of relative number of excess anions required to for typical resting potentials is small compared to the total number of ions in a cell.
6. Understand that bulk solutions are always electrically neutral.
7. Describe electro-chemical gradients in a cell and how cells exist in equilibrium.
8. Apply osmotic balance, charge neutrality, Donnan Equilibrium and the Nernst equation to calculate ion concentrations and the membrane potential of an artificial cell.
9. Understand how membrane potential depends on relative, not absolute, permeabilities to ions.
10. Define Driving Force on an ion.
11. Describe why, in neurons and other excitable cells, membrane potential is sensitive to small changes in $[K^+]_o$, but not $[Na^+]_o$.
12. Describe two treatments for hyperkalemia by which cells can be encouraged to take up potassium from the ECF.

Membrane Structure

1. Describe the molecular components of a membrane and identify the parts of a phospholipid, sphingolipid, and cholesterol.
2. Describe the concept of membrane fluidity.
3. Describe the asymmetry of membrane bilayers and provide at least two reasons that this asymmetry is functionally important.
4. Describe the different ways proteins associate with membranes.
5. Provide an explanation for the genetic basis of familial hypercholesterolemia, its relation to atherosclerosis, and the treatment for this disease.
6. Explain how cholesterol synthesis is regulated by gene transcription, cholesterol sensing in the ER and transcription factor release in the Golgi and the role of statins in this pathway.

Membrane Transporters

1. Describe the difference between primary and secondary active transport.
2. Define cotransport and exchange transport.
3. Identify physical forces that can determine the gating properties of ion channel.
4. Determine if a pump for a particular ion must exist in a cell at rest (steady state), given an ion's concentration inside and out, the membrane potential, and knowledge that the membrane is permeable to the ion in question; and, if a pump must exist, determine which direction it pumps the ion.
5. Describe how cells concentrate glucose inside, even though the glucose transporter cannot pump glucose against its concentration gradient.
6. Understand the mechanism of Digitalis.

Mitochondria

1. Explain the origin, basic structure and fission/fusion of mitochondria.
2. Explain the basic machinery of mitochondria import.
3. Explain the basic principles of electron transport and ATP production in mitochondria.
4. Explain the basic mechanisms of cell death regulation by mitochondria.
5. Recognize and correctly diagnose clinical presentations of mitochondrial disease.

Mitosis and Cell Cycle I

1. Understand that stem cells cycle and when/why; contrast with "terminally differentiated" cells.
2. Describe how cyclins and cyclin-dependent kinases drive each phase of the cell cycle and define how levels of these are controlled.
3. Recognize the importance and the mechanism of cell cycle checkpoints in maintaining genomic stability.
4. Describe how cells prevent re-replication of their genomes by keeping the assembly and activation of replication complexes in separate cell cycle phases.
5. Recognize that genomic instability either by chromosome re-replication in S phase or mis-segregation during mitosis produces human diseases such as cancer and birth defects (trisomy 21).
6. Compare the cell cycle of somatic cells (mitosis) with that of germ line cells (meiosis), which produces haploid gametes.
7. Describe how alterations in many cell cycle regulators that are found in cancer cells are being used for patient diagnosis and prognosis.

Mitosis and Cell Cycle II

1. Compare the cell cycle of somatic cells (mitosis) with that of germ line cells (meiosis), which produces haploid gametes.
2. Recognize that differentiated, post-mitotic cells such as neurons are stuck at the "R" point in that they continue to grow without cycling.
3. Describe how alterations in many cell cycle regulators that are found in cancer cells are being used for patient diagnosis and prognosis.
4. Recognize the importance and the mechanism of cell cycle checkpoints in maintaining genomic stability.

Molecular Basis of Carcinogenesis I

1. Describe at least five different properties of malignant cancer cells.
2. Describe the multi-step process for carcinogenesis, and discuss the relative importance of heredity and the environment and why early events may include mutations in DNA repair genes.
3. Discuss the types of genes usually mutated in tumor initiation and their effect on cellular proliferation.
4. Describe at least two different examples for the type of cytogenetic abnormalities associated with malignancy.
5. Give at least two examples of events that can produce loss of heterozygosity and how they support Knudson's theory.
6. Describe how cancers are associated with both dominant and recessive syndromes.
7. Describe how the RB protein functions during the cell cycle and why it is important in cancer, specifically how the loss of RB may produce a malignancy.

Molecular Basis of Carcinogenesis II

1. Explain why APC, BRCA1 and BRCA2 genes are tumor suppressors.
2. Describe the cellular function of the p53 protein.
3. Recognize that oncogenic viruses make proteins to inactivate both Rb and p53, using HPV (human papilloma virus) as an example.

Molecular Basis of Carcinogenesis III

1. Discuss the functions of protein products of viral oncogenes, including at least four examples of oncogenes.
2. Describe why oncogenes are useful as molecular markers in prognosis and discuss at least two examples of oncogenes that are currently being used, including the evidence of why these are good markers.
3. Describe two examples of how molecular, genomic, and clinical information (Bioinformatics) about a patient's cancer are being used for targeted therapy and for "personalized medicine" in cancer.

Molecular Cytogenetics

1. Recognize two of the most common leukemia translocations - one in chronic myeloid leukemia (CML) and one in acute promyelocytic leukemia (AP), and discuss the importance of these chromosomal findings that lead to biologically-based, targeted therapy (it's all in the genes!).
2. Describe the common cytogenetic findings in childhood B-cell leukemia and how the cytogenetic findings influence patient prognosis.
3. Delineate types of fluorescence in situ hybridization (FISH) probes and how they complement standard cytogenetic analysis, particularly in hematologic malignancies.
4. Explain the roles of chromosomal microarray (CMA) analysis in aiding certain genetic diagnoses and explain why CMA testing can detect genomic deletions or duplications, but not translocations.
5. Recognize and use laboratory-testing algorithms for children who present with learning disorders, developmental delays, autism, dysmorphic features, and/or failure to thrive.

Molecular Genetics of Hemoglobinopathies

1. Describe the genetic features of the α - and β -globin gene cluster, the locus control regions, and the control of globin switching during development.
2. Explain the disease-causing mutations and consequences of sickle cell anemia, hemoglobin C disease, β^0 -thalassemia, β^+ -thalassemia, simple β -thalassemia, and complex β -thalassemia.
3. Know the six possible genotypes of α -globin locus, their clinical phenotypes, and the geographical distributions of α -thal-1 (--) and α -thal-2 (α^-) alleles.
4. Explain the types of mutations that can cause hereditary persistence of fetal hemoglobin and its clinical implications.

MTOR

1. Describe the role of the PI3-kinase/Akt/mTOR pathway in normal cell function.
2. Describe the role of the PI3-kinase/Akt/mTOR pathway in cancer.
3. Discuss the role of mTOR inhibitors in clinical practice.
4. Discuss the impact of TSC1/2 mutations.

Multifactorial Inheritance

1. Identify and describe the characteristics of diseases and other traits that demonstrate multifactorial inheritance.
2. Give specific examples of diseases and other traits that demonstrate multifactorial inheritance.
3. Describe the strategies used to determine the relative importance of genetic vs. non-genetic factors in contributing to the variation in a complex trait.
4. Recognize and discuss the potential difficulties associated with quantifying the role of genetic factors in contributing to risk of disease at both the population level and the individual level.

Muscle I

1. Explain the structural basis of skeletal muscle contraction by constructing a sarcomere.
2. Describe the two regulatory proteins; specifically, where they are located and how they respond to changes in calcium concentration.
3. Describe the length of a sarcomere in resting muscle, contractile muscle, and muscle that is stretched almost to the point of injury (tearing) and discuss how this addresses the ambiguity of the question - "what is the length of a sarcomere?"
4. Describe the molecular basis of skeletal muscle diversity (fast and slow fibers) and the value of having this additional complexity.
5. Describe the key structural and physiological features of cardiac muscle and how they are similar to and different from skeletal muscle (sarcomere, regulatory proteins, events involved in a single contraction and relaxation, response to injury).
6. Explain why smooth muscle appears smooth and describe the key structural and physiological features of smooth muscle and how they compare to skeletal and cardiac muscle (contractile proteins, regulation of contraction, cell organization).
7. Describe how skeletal muscle develops (single cells going to multinucleate cells).
8. Explain the importance of the signaling protein myostatin and the consequences of mutations of myostatin.
9. Explain the molecular basis of familial hypertrophic cardiac myopathy, including the mutated proteins associated with this myopathy.

Muscle II

1. Explain how excitation-contraction coupling is accomplished for skeletal, cardiac and smooth muscle and why the t-system is not required in smooth muscle.
2. Define a myofibril and describe the relationship between myofibrils and the sarcoplasmic reticulum.
3. Starting with an action potential in a motor neuron, explain the processes required to have a skeletal muscle undergo a single contraction and relaxation (a twitch).
4. Explain the reason for the transverse-tubule system (t-system) in skeletal and cardiac muscle and how excitation-contraction coupling is accomplished in skeletal muscle.
5. Identify where motor nerve terminals associate with skeletal muscle fibers and describe the distribution of cells innervated by one motor neuron in a muscle.
6. Explain the molecular basis of malignant hyperthermia, the related protein mutation, the reason for the temperature rise, and the type of compound that will prevent the temperature rise.
7. Discuss the physiological and biochemical basis of skeletal muscle contraction, how contractile proteins work, and how they are regulated in skeletal muscle.

Muscle III

1. Identify muscle types that contain gap junctions and explain the role of gap junctions in these muscles.
2. Describe how tension is graded in cardiac and smooth muscle (two mechanisms) and how this is different from the gradation of tension for skeletal muscle.
3. Describe a muscle motor unit and how its average size relates to the function of that muscle.
4. Describe the two major mechanisms for how skeletal muscle tension is graded and regulated.
5. Define the role of "satellite cells" in skeletal muscle development and repair.
6. Describe the physiological and structural responses to exercise (or lack of exercise) on skeletal muscle (number of cells versus size of cells).
7. Explain the genetic and molecular basis of Duchenne muscular dystrophy, including the mutated protein associated with this myopathy and how this protein contributes to muscle structural integrity.

Muscular Dystrophy w/Patient Vignette

1. For the following three conditions, Hypertrophic cardiomyopathy, Malignant hyperthermia, and Duchenne Muscular Dystrophy:
 - a) Recognize and distinguish the above phenotypes in patients.
 - b) Explain how the molecular defect causes the abnormal muscle cell phenotype.
2. Identify and explain the triggers and treatment of malignant hyperthermia.
3. Describe the potential role of the manipulation of myostatin function in the treatment of muscular dystrophies.

Mutational Mechanisms and Disease

1. Describe, distinguish between, and give examples of the four major mechanisms that genetic mutations lead to disease: 1) loss of function of the protein (most common), 2) gain of function of the protein, 3) acquisition of a novel property by the mutant protein, and 4) perturbed expression of a gene at the wrong time (heterochronic expression) or in the wrong place (ectopic expression), or both.
2. Provide, discuss, and explain examples of the eight steps at which mutations can disrupt the production of a normal protein as presented in your text.
3. Describe and explain the mechanism of genetic anticipation in tri/tetra-nucleotide repeat disorders and recognize the phenotypes of these disorders.

NextGen Sequencing

1. Describe the major types of next-generation DNA sequencing.
2. Compare and contrast the types of data that next-generation DNA sequencers produce, in terms of read number and error rates.
3. Explain the key criteria that must be considered during analysis of next-generation DNA sequencing data for SNP identification.
4. Describe exome sequencing experiments and explain types of mutations that can be detected with this strategy.
5. Describe which types of diseases are best characterized by exome sequencing and which types of diseases are not diagnosable by exome sequencing.

Non-Coding Regulatory RNAs

1. Define and distinguish among miRNAs, siRNAs, and long non-coding RNAs.
2. Describe the biogenesis, mechanism of action, and functions of non-coding RNAs.
3. Describe the efforts and issues associated with using regulatory RNAs for treatment.
4. Describe antisense oligonucleotide therapeutics and their mechanisms of action.
5. Describe an example of a disease that might be treatable with small RNAs, how it would be treated, and the limitations.

Nucleus and Nuclear Import and Export

1. Describe the structure of the nuclear pore complex and roles of nucleoporins (Nups), karyopherins, and Ran in nuclear transport.
2. Describe the basic mechanisms of nuclear import and export of proteins and RNA/protein complexes, and how they can be regulated.
3. Explain how changes that impact nuclear transport and/or NPC components can contribute to disease.

Pedigree Analysis

1. Apply and interpret common family history (pedigree) symbols.
2. Collect family history data and draw a 3-generation family history using standard pedigree symbols.
3. Populate a family history with relevant medical phenotype information.
4. Discuss how the distribution of phenotypes in a pedigree is a reflection of the segregation of gene variants (genotypes).
5. Discuss potential ethical issues in the use and disclosure of pedigree information.

Peroxisomal Disorders

1. Describe the basic functions of the peroxisome.
2. Explain the concept of an inborn error of metabolism, and in particular how a single genetic defect may manifest as a multi-systemic disorder of peroxisomal metabolism.
3. Identify clinical features, causative genes, and potential therapies of several common Peroxisomal disorders including Zellweger spectrum disorders, Rhizomelic Chondrodysplasia Punctata Type 1, and X-linked Adrenoleukodystrophy.

Pharmacogenetics

1. Define and distinguish between pharmacogenetics and pharmacogenomics.
2. Explain the two major physiologic responses to drugs, pharmacokinetics and pharmacodynamics, and briefly contrast Phase I and Phase II drug metabolism steps.
3. Explain the central role of the polymorphic CYP450 enzyme system in drug metabolism.
4. Recognize and understand key specific pharmacogenetic examples.
5. Recognize the truism of the axiom "Variety is the spice of life!"

Population Genetics

1. Define the field of population genetics and explain why "population" field has relevance to doctors who often treat just "one patient" at a time.
2. Apply basic principles of population genetics (estimate mutation rates, determine fitness, and understand effects of consanguinity and the addition of new mutations to gene pool).
3. Explain and discuss the assumptions required for Hardy-Weinberg principle to apply.
4. Apply the Hardy-Weinberg principle to estimate carrier frequencies for autosomal recessive disorders.
5. Discuss how physicians managing genetic diseases could affect the prevalence of genetic diseases.

Prader-Willi Vignette

1. Describe the chromosomal 15 abnormalities that can lead to Prader-Willi Syndrome (PWS) and how to test for them.
2. Describe the physical features (Phenotype) seen in patients with Prader-Willi Syndrome.
3. Describe the role of imprinting in disorders involving chromosome 15.
4. Describe the medical problems seen in patients with Prader-Willi Syndrome.
5. Recognize and describe the developmental and behavioral phenotypes of patients with Prader-Willi Syndrome.
6. Describe other common disorders associated with abnormalities on Chromosome 15q.

Prion Vignette

1. Explain the relationship between structures of the prion protein (PrP) and the infectious agents known as prions.
2. Describe how prion disease can be sporadic, inherited or infectiously acquired.
3. Explain the possible relationship between prion disease and other human neurodegenerative diseases, at the level of protein structure.
4. Understand the biochemical basis of new diagnostic tests for prion diseases.

RNA

1. Compare and contrast structural RNAs (ribosomal, transfer, small nuclear, small nucleolar), information containing RNAs (messenger), and regulatory RNAs (micro, small interfering).
2. Compare and contrast RNA to DNA (ability to be hydrolyzed, single vs. double stranded, folding and secondary structure).
3. Give examples of ribonucleoprotein complexes and their implications for disease and therapy.

RNA Synthesis and Splicing

1. Describe the mechanism of DNA-directed RNA synthesis (i.e. transcription) in terms of initiation, elongation, and termination.
2. Compare and contrast transcription as performed by bacterial and eukaryotic polymerases.
3. Compare and contrast the four main RNA polymerases.
4. Define the roles played by control elements on DNA (promoters, enhancers, repressors) and transcription factors that modulate RNA transcription.
5. Describe unique attributes of the C-terminal domain of RNA polymerase II that affect RNA transcription.
6. Describe diseases and syndromes caused by defects in transcription.
7. Describe the 3 major steps of pre-mRNA processing: capping, splicing, polyadenylation and their functional consequences.
8. Define the functions of the cap, splicing, and polyA tail.
9. Describe how alternative splicing facilitates the expression of isoforms of genes ($\geq 10^6$ mRNAs), thus amplifying an "economic" genome of only 10^3 genes.
10. Give examples of disorders caused by splicing defects.

Secretory Pathways I & II

1. Describe the three mechanisms of protein transport.
2. List the major functions of the endoplasmic reticulum (ER).
3. Describe co-translational translocation for the synthesis of cargo and transmembrane proteins.
4. List the major functions of the Golgi.
5. Name three well-studied vesicle coats and describe how these coats function in vesicular transport.
6. Explain the importance of protein retrograde movement from the Golgi back to the ER; describe one molecular mechanism for the retrograde movement.

Signaling Receptors

1. Describe the membrane topology a G protein-coupled receptor and identify the basic structural characteristics that mediate ligand binding and coupling to G proteins.
2. Explain how G protein-coupled receptors activate hetero-trimeric G proteins and diagram the GTP-hydrolysis cycle of G protein signaling.
3. Describe the function of second messengers in receptor signaling and give two examples for how they are generated by activated G proteins.
4. Explain how G-protein-coupled receptor activation leads to signal termination through receptor desensitization and coupling to additional pathways.
5. Give two examples of drugs that act through modulating different steps in a G protein-coupled receptor second messenger signaling cascade.

Signaling: Serine-Threonine Kinases and Phosphatases

1. Describe a phosphorylation reaction (including which amino acids can be phosphorylated) and explain how it can affect a phosphorylated protein.
2. List at least two other types of secondary protein modification
3. Explain the structure of an ATP molecule.
4. Explain how protein kinases can be classified and describe examples.
5. Describe the structure/function of a protein kinase and principles of their regulation (including requirement for activation loop phosphorylation in some but not all kinases).

Stem Cells & Differentiation (No In-Class Lecture; Panopto Only)

1. Explain the basics of stem cells, their niches, and the commitment (differentiation) of stem cells into different lineages.
2. Explain the concept of adult stem cell plasticity.
3. Explain the concept of reprogramming adult somatic cells into induced pluripotent stem (iPS) cells or embryonic-like stem cells.
4. Describe the role of stem cells in the initiation and maintenance of cancer.

Thalassemia Vignette

1. Recognize quantitative and qualitative changes in human globin chains.
2. Describe the geographic distribution of the common hemoglobin variants.
3. Identify the clinical and genetic features of β thalassemia syndromes.
4. Identify the clinical and genetic features of α thalassemia syndrome.

Toll-Like Receptors

1. Define and explain the terms Pathogen Associated Molecular Pattern (PAMP) and Pathogen Recognition Receptor (PRR).
2. Match different Toll-like receptors with their cognate Pathogen Associated Molecular Pattern proteins.
3. Describe the basics of Toll-like receptor signaling pathways.
4. List examples of key genes and pathways activated by Toll-like receptor signaling.
5. Explain the importance of subcellular localization of Toll-like receptors.
6. Explain, and provide examples of, how Toll-like receptor signaling is relevant for human infectious and inflammatory disease.
7. Provide examples of how Toll-like receptor agonists can be used therapeutically.
8. Provide examples of how Toll-like receptor antagonists can be used therapeutically.

Tools of Molecular Biology I & II

1. Describe distinct uses of PCR amplification in the diagnosis of a genetic condition in patients.
2. Describe the use of microarrays for measuring levels of mRNA gene expression and their implications for diagnosis and treatment.
3. Give an example of a disease that can be diagnosed using a restriction fragment length polymorphism (RFLP) and a use of DNA fingerprinting. Describe at least three experimental stages required in each of these procedures.
4. Define “personalized medicine” from the perspective of molecular and cell biology and give an example using cancer screening.
5. Describe the process of producing recombinant proteins and provide examples of their utility in medicine.
6. Describe standard approaches used in recombinant molecular biology approaches to: a) copy a DNA sequence into a DNA sequence, b) copy an RNA sequence into a DNA sequence, and c) join DNA fragments.
7. Explain the principles of electrophoretic separation and analysis of DNA, RNA, and protein targets.
8. Describe different types of cloning vectors and their general applications.

Translation I & II

1. Name and describe the roles of the parts of the machinery that drives translation, specifically: ribosomes, mRNA, tRNA, aminoacyl tRNA synthetases, initiation factors, elongation factors, and release factors.
2. Be able to explain the nature of the genetic code, how it is read, and the effects of mutations to the mRNA. Name the start codon and what amino acid it encodes.
3. Describe the four phases of translation: initiation, elongation, termination, and ribosome recycling, and describe the basic elongation cycle.
4. Compare and contrast the important differences between bacterial and eukaryotic translation, especially in regard to initiation.
5. Identify antibiotics that operate by affecting translation.
6. Explain the significance and effects of the following processes: cap-independent initiation, interferon stimulation, mRNA editing, rapamycin treatment, eIF2-alpha phosphorylation. Be able to describe when these might be important.

Treatment of Genetic Diseases

1. Discuss and explain that while curing genetic diseases remains challenging, many genetic diseases are amenable to some level of treatment/management.
2. Identify genetic conditions that currently can be treated and describe strategies and specific examples for treating genetic diseases.
3. Discuss and explain examples of genetic disorders that are treated on the basis of protein/enzyme replacement therapy.
4. Identify and explain the principles and theoretical risks of different gene therapy approaches.
5. Identify the financial, ethical, social, economic and legal issues raised by specific therapies for genetic illnesses.

Turner Syndrome Vignette (No Lecture; Panopto Video Available)

1. Recognize the clinical presentation of patients with Turner Syndrome.
2. Enumerate medical, social, and psychological challenges across the lifespan in patients with Turner Syndrome.
3. Identify pitfalls of the medical culture in addressing the needs of patients with Turner Syndrome.

Tyrosine Receptor Kinases

1. Describe mechanism of receptor tyrosine kinase (RTK) activation.
2. Explain molecular mechanism of stimulation of ras GTPase by receptor tyrosine kinases.
3. Describe mechanism of action of two main classes of RTK-targeted anti-cancer agents (antibodies and TKI's).
4. List tumor cell characteristics that predict clinical response to EGFR-targeted therapeutics.
5. Describe mechanism of resistance to TKI's such as EGFR inhibitors.

Vasculature

1. Describe the structure, organization, and function of the basic layers of blood vessel walls.
2. Discuss the morphological characteristics that distinguish the different types of blood vessels.
3. Explain the structure and function of the different types of capillaries.
4. Outline the unique functions of post-capillary venules.
5. Describe how blood flow is regulated in capillary beds.
6. Discuss the general structure and functional significance of arterio-venous shunts, portal systems, pampiniform plexus, anastomoses, and end arteries.

Von Hippel-Lindau Clinical Vignette

1. Describe the clinical manifestations of Von Hippel-Lindau (VHL) disease.
2. Describe the molecular basis of Von Hippel-Lindau (VHL) disease and the pathogenesis of clear cell renal cell carcinoma.
3. Describe the molecular rationale for therapies used to treat clear cell renal cell carcinoma and how these targets were identified through understanding diseases such as VHL.

X-Linked Recessive Inheritance and Mitochondrial Diseases

1. Distinguish and explain the differences between X-linked dominant and X-linked recessive inheritance patterns.
2. Describe the characteristics and genetic inheritance mechanisms of an X-linked pedigree.
3. Describe the general features of mitochondrial inheritance and the clinical manifestations of mitochondrial diseases.
4. Recognize and describe the clinical features and molecular basis of Hemophilia A, Duchenne Muscular Dystrophy and Fragile X Syndrome.
5. Describe and explain X chromosomal inactivation and its complications.