I. MCBG, MEDICAL KNOWLEDGE OUTCOME OBJECTIVES

The unprecedented and accelerating expansion of knowledge concerning the molecular and genetic basis of human disease is expected to continue to produce rapid changes in how physicians define, diagnose and treat illness during the lifetimes of our graduates. The following elements of knowledge in MCBG have been defined as essential because they are judged either to be relevant to current practices, to have a significant potential to be translated into new treatments in the near term, or to be needed by future physicians to help them to acquire new knowledge to maintain their clinical effectiveness. In addition, MCBG has a responsibility to prepare or students for board exams that may be used by residency programs in applicant selection. With these in mind, students are expected to be able to discuss, explain, interpret or utilize clinically each of the following:

Proteins and Enzymes

1. Properties of common amino acids and how they relate to protein structure and function, basic concepts of protein structure (motif, fold and domain), and the effects of mutation on protein structure and function, with examples.
2. Structural basis for cooperativity in oxygen binding to hemoglobin
3. The Bohr Effect, its relation to oxygen binding and the ability of hemoglobin to buffer transient changes in blood pH.
4. The transport of CO_2 by blood and the role of hemoglobin in CO_2 transport.
5. The effects of mutation on hemoglobin function and solubility with Sickle Cell Disease and other hemoglobinopathies as examples
6. The structure of type I collagen and the effect of mutation on collagen structure and function.
7. The Henderson-Hasselbalch equation and its use in predicting the state of ionization and charge of amino acids and small peptides, and the activities of proteins and enzymes that contain ionizable amino acid side chains essential to their function.
8. Principles and techniques of electrophoresis and isoelectric focusing to separate and analyze proteins, and the application of these techniques to the identification of abnormal protein expression patterns for the diagnosis of cancer and other human disorders.
9. Principles of enzyme function and catalysis, mechanisms by which enzyme activity can be altered by inhibitors and drugs, and comparisons of competitive inhibitors, noncompetitive inhibitors and irreversible inhibitors with respect to their ability to affect or be effected by substrate binding and/or rates of product formation.
10. Analysis and interpretation of data and graphs to solve problems related to protein expression and function, enzyme catalysis, and malfunctions of these processes

Molecular Biology/Molecular Genetics

11. The mechanisms and principles related to the body of knowledge described by the terms Molecular Biology and Molecular Genetics, including chromatin structure and how it may be modified to affect gene expression and repression, DNA replication and repair, DNA recombination, RNA synthesis and processing, and protein synthesis. This includes:
12. The structures of teleomeres, centromeres and origins of replication as features of human chromosomes essential for their replication and segregation during mitosis.
13. How DNA in chromosomes is replicated by DNA polymerases in a manner that minimizes copy errors, and how copy errors or other forms of DNA damage are repaired, and how DNA undergoes recombination during meiosis.
14. The role of telomerase in generating the ends of chromosomes during chromosomal replication in germ cells and the relationship between the expression of telomerase, cellular senescence and cancer.

15. The role of histones and other DNA binding proteins in the packaging of DNA in chromosomes (chromatin).
16. How modifications of histones generate epigenetic marks that define cell type.
17. The mechanisms by which DNA is transcribed into RNA, including the role of gene promoters, the function of RNA polymerase II, basal transcription factors (TATA binding protein and its associated factors), and common transcriptional regulators such as Myc, AP1 and Sp1, whose levels or activities are frequently elevated in cancer.
18. The mechanisms by which chromatin remodeling complexes (e.g. SWI/SNF), enzymes that modify histones (e.g acetylases and kinases), and transcription factors act synergistically to alter chromatin structure and regulate gene expression.
19. How enzymes that modify DNA (methylases) and histones (acetylases, deacetylases and methylases) act to regulate gene expression, and generate epigenetic marks that define cell type during differentiation; mechanisms that exist for transmitting these epigenetic marks to daughter cells in order to maintain the differentiated state following replication
20. Mechanisms by which newly made RNA transcripts are processed (capping, polyadenylation and splicing) to produce mature, functional messenger RNAs
21. The major components of the protein synthesis machinery – tRNAs, aminoacyl-tRNA synthetases, ribosomes, translation factors – and the individual steps in translation that may be subject to regulation
22. How changes in chromosome number and DNA structure might occur, and their possible effects on the levels and activities of proteins.
23. The principles and techniques used to separate, identify, manipulate and analyze DNA, and to measure the expression of RNA.
24. How accuracy in protein synthesis is achieved, including the roles of aminoacyl-tRNA synthetases, key translation initiation factors and the ribosome.
25. Mechanisms by which gene expression is regulated after transcription, including:
    - The regulation of alternative pre-mRNA splicing to produce multiple forms of a protein from a single gene
    - the phosphorylation of translation initiation factors in response to anabolic hormones, growth factors, and in cancer (activation), and during cellular stress (inhibition)
    - the regulation of mRNA levels and/or activities by microRNAs (miRNAs) and the relationship between changes in miRNA levels and cancer
    - the pathway and machinery that participate in the regulated destruction of proteins – the ubiquitin conjugating system and the proteasome – and their relationship to inherited and acquired neurodegenerative disorders associated with aging.
26. Analysis and interpretation of data to solve problems based on the application of molecular genetic techniques to the detection and study of human disease.

Human Genetics

27. The nature and origins of genetic variation in humans, the relationship between genes and disease, the variations in the frequencies of mutant alleles between different human populations
28. Application of the Hardy-Weinberg law to calculate genotype and phenotype frequencies from allele frequencies in a population and to apply the Hardy-Weinberg law in medical genetics and genetic counseling
29. Produce a family pedigree from a family history, and to distinguish patterns of inheritance for single gene disorders linked to autosomes, sex chromosomes and mitochondrial genes.

30. The methods used to determine the relative contribution of genes and environment for common disorders with complex inheritance, and the use of empirically derived risk tables in genetic counseling.
31. The principles and techniques used in clinical cytogenetics – karyotyping, fluorescence in situ hybridization (FISH), and chromosome painting – to detect abnormalities in chromosome number and structure, and the clinical indications for their use.
32. The etiology, pathogenesis, phenotype and natural history, management, and inheritance risk of some common disorders that illustrate important genetic principles.

Cell Structure and Biology

33. The composition, organization and properties of biological membranes, the mechanisms and roles of transport proteins and ion channels that conduct active and facilitated transport, and their roles in creating an electrical potential across the plasma membrane.
34. The mechanism by which an action potential is initiated and propagated along a neuron, and the events that occur at the synapses between neurons and at neuromuscular junctions.
35. The appearance, properties and functions of various cytoskeletal elements and organelles in eukaryotic cells, including microtubules, actin filaments, and thin filaments, the nucleus, mitochondria, the endoplasmic reticulum, Golgi apparatus, endosomes, lysosomes and peroxisomes.
36. The mechanisms by which various membrane-bound organelles incorporate newly made lipids and proteins needed for their maintenance and propagation.
37. The mechanism and regulation of the transport of RNA and proteins through the nuclear pore by the GTP binding protein, Ran, and its relationship to the regulation of gene expression
38. The mechanisms and components of vesicular transport by which proteins move through the endocytic and secretory pathways in cells, including the role of regulatory GTP binding proteins (Arf, Sar, and Rabs), vesicle coat proteins (clathrin, adaptin, COP I and COP II), membrane specific phosphoinositides, and snares.
39. The role of receptor-mediated endocytosis in the uptake of LDL and other extracellular proteins, and in the termination of signaling from hormone receptors.
40. The role of the cytoskeletal proteins actin and tubulin, and their associated motor proteins in vesicular transport, mitosis and meiosis, and explain how these proteins contribute to the shape, internal architecture and motility of cells.
41. Intracellular signaling pathways initiated by hormones and other extracellular signaling molecules that bind to G-protein coupled receptors, the trimeric GTP binding proteins with which they interact, G_s, G_q, or G_i, and their downstream effectors, e.g.
    - adenyl cyclase, cAMP and protein kinase A, and the mechanism and physiological results of cholera toxin effects on cAMP in intestinal epithelial cells
    - diacylglycerol and protein kinase C;
    - phosphospholipase C-β, IP_3, calcium, calmodulin and CaM-kinases; and calcium-calmodulin, nitric oxide synthase (NOS), NO, guanylcyclase, cGMP, and protein kinase G, and the mechanism and effects of the cGMP phosphodiesterase inhibitor, sildenafil citrate, on vascular smooth muscle cells.
42. The role of nuclear receptors in transmitting signals from steroid hormones and other hydrophobic agonists that can diffuse across the cell membrane.
43. The types of microscopes, staining techniques and methods of specimen preparation used to study normal and abnormal tissues, and the uses and advantages of each.

44. The structure, composition and synthesis of the extracellular matrix and its constituents, and the identities and properties of the various junctions by which cells contact the extracellular matrix and each other in tissues, using epithelium as the example.
45. Describe the serous epithelial surfaces that line the pleural, pericardial, and abdominopelvic cavities (cross listed with SHB).
46. The identities, functions and appearances of cells and other tissue components that comprise dense regular connective tissue such as tendon, ligament, and bone) (cross-listed with SHB)
47. Describe the histology of skin (cross-listed with SHB).

The Cell Cycle, Mitosis, Apoptosis and Cancer

48. The cell cycle and its stages, the cell cycle control or checkpoints at which the cycle is regulated, and key regulators and mechanisms that control the progression of cells through cycle. This includes:
    - the roles of the cyclins and the cyclin-dependent kinases (cdks);
    - the Cdk regulatory kinases (e.g. the CAKs and Wee1) and phosphatases (cdc25) as regulators of Cdk-cyclin activities;
    - the functions of the ubiquitination protein ligases SCF and APC (anaphase promoting complex) in the regulation of the cell cycle; and
    - the role of cyclin-dependent kinase inhibitors (CKIs) such as p27 and p21 in regulation of the cell cycle, and why the loss of p27 or p21 expression can contribute to cancer.
49. The relationship between the cell cycle dysregulation and cancer. This includes:
    - the role of the transcription factor E2F in cellular replication, and its regulation by Rb protein and oncogenic DNA viruses;
    - the central role of p53 and the p53 regulatory network in the regulation (inhibition) of cell replication and the induction of apoptosis in response to DNA damage;
    - the targeted (proteasome-mediated) degradation of p53 by kinases, phosphatases and the ubiquitin protein ligase Mdm2;
    - the relationship between DNA viruses, E2F activation, cell cycle progression and cancer; and
    - the mechanisms by which the loss of expression of Rb, p53 or components of the p53 regulatory networks contribute to cancer, and their frequency in human cancers.
50. The individual phases of mitosis – prophase, prometaphase, metaphase, anaphase, telophase and cytokinesis – and the major regulatory events and checkpoints associated with each phase.
51. The structures of kinetocores, centrosomes, centrioles, microtubules and molecular motors in the formation of the mitotic spindle and the movement of chromosomes to opposite poles of the dividing cell during anaphase.
52. The role of the mitotic cyclin-dependent kinase (M-Cdk) in the regulation of mitosis and the assembly of the mitotic spindle
53. The role of the ubiquitin protein ligase APC (see also 46) and its regulatory subunit cdc20 in regulating the separation of sister chromatids during anaphase
54. The spindle assembly checkpoint, the potential consequences of its dysregulation, and the possible relationship between spindle checkpoint irregularities and the aneuploidies often observed in human cancers
55. The mechanism by which growth factor receptor tyrosine kinases transmit the mitogenic signals that cause the target cell to enter the cell cycle, including:

- SH2 and SH3 domains as protein interaction domains that mediate binding between receptors, their interacting partners (scaffold and adaptor proteins), and downstream effectors to effect the activation of multiple parallel intracellular signaling pathways;
- the function of important components of the Ras signaling pathway and their functions, including Grb-2, Sos (guanine nucleotide exchange factor or GEF specific for Ras), Ras, and the downstream cascade of mitogen activated protein kinases;
- the identity of important components of the PI-3 kinase signaling pathway and their function including PI 3-kinase, PDK1, Akt and mTOR, and the inhibitory phosphatase, PTEN;
- the effects of mutations that lead to the constitutive activation of Ras or the inactivation of PTEN on the development of cancer; and
- the targets of growth factor receptor signaling pathways, their role in regulating progression through the cell cycle, and their potential as targets for drug development.

56. The apoptotic pathways and mechanism by which cells undergo controlled death, the key internal and external regulators of apoptosis, and the relationship between dysregulated apoptosis and cancer, including:
    - the central role of mitochondria, its release of cytochrome c, the formation of the apoptosome (Apaf1) and the activation of a caspase cascade in apoptosis;
    - the role of Bcl2 and Bcl-X_L and negative regulators of cytochrome c release;
    - the roles of Bid, Bad, Bak and Bad in promoting the release of cytochrome c and the initiation of apoptosis;
    - the role of p53 in the activation of apoptosis following DNA damage; and
    - the role of the death receptor pathway activated by Tumor Necrosis Factor-α (TNF- α) and FAS receptors in promoting apopotosis
57. The role of mutation and environmental agents in forming cancers, including oncogenic viruses, growth-promoting chemicals and DNA damaging agents.
58. The types of changes in protooncogenes and tumor suppressor genes that are needed to occur at each stage in the progression of a normal cell to a malignant cancer cells, including:
    - the mechanisms by which tumor cells become immortal, metastasize and grow, and the role of angiogenesis and its regulators in promoting tumor growth;
    - the growth factor receptors and components of growth factor receptor signaling pathways and their regulators as oncogene and tumor suppressor gene products, and as potential targets for drug development in the treatment of cancer; and
    - the genetic and epigenetic heterogeneity of cancers as the basis for the use of personalized biochemical analysis in forming a prognosis and treatment protocol for a particular cancer.
59. The interpretation of elementary data related to the toxicity and efficacy of targeted drug therapies obtained from studies involving cultured cells, animal models and clinical trials in humans.

Methods of evaluation: Multiple choice exams, small group problem solving sessions, student presentations on genetic disorders, and laboratory exercises when appropriate.

II. INTERPERSONAL AND COMMUNICATION SKILLS

By the end of this course, students must have demonstrated knowledge of the basic principles of effective interpersonal communication, and the skills and attitudes that allow effective interaction with their peers, faculty, and support staff. Students will:

1. Use verbal language effectively.
2. Use effective listening skills and elicit and provide information using effective nonverbal, explanatory, and questioning skills.
3. Use written language effectively.
4. Facilitate the learning of other students, including giving effective feedback.
5. Communicate essential information effectively within their small group and with other students in the class.

Methods of evaluation: Small group problem solving sessions, evaluation of oral presentations

III. LIFELONG LEARNING, PROBLEM-SOLVING AND PERSONAL GROWTH

By the end of this course students must demonstrate the knowledge, skills and attitudes needed to be able to use appropriate tools of evidence to identify and analyze books, reviews, online resources, and basic science reports for their applicability towards quality in healthcare and quality improvement. Students will:

1. Apply acquired knowledge effectively.
2. Locate, appraise, critically review and assimilate evidence from scientific studies and medical literature.
3. Use information technology learning resources to manage basic science information, access online information and support their own education.
4. Demonstrate an investigatory and analytic thinking approach in SGPSS and course projects.
5. Demonstrate a commitment to individual, professional and personal growth.

Methods of evaluation: Small group problem solving sessions, student presentations on genetic disorders, review of the technology resources and search strategies used by students to gather information, review of annotated bibliographies describing how students used information to prepare their presentations.

IV. PROFESSIONALISM, MORAL REASONING AND ETHICAL JUDGEMENT

By the end of this course, students must demonstrate a combination of knowledge, skills, attitudes, and behaviors necessary to function as a respected member of a learning team in both small group and large class settings. Students will:

1. Behave professionally in the context of the small group problem-solving session, including attendance, punctuality, preparedness, and ability to interact effectively with other small group members in the educational setting.
2. Recognize and effectively deal with unethical behavior of other members of the class, if encountered.

Methods of evaluation: Small group problem solving sessions, general observation of student behavior.