Molecular Medicine
Learning objectives for candidates preparing for the Wits Additional Placement Test (WAPT) – 2019

REFERENCES
Textbooks
 Marieb EN, Hoehn K. Human anatomy & physiology (10th ed.) San Francisco: Pearson/ Benjamin Cummings
 Marieb EN. Essentials of human anatomy & physiology (11th ed.) San Francisco: Pearson/ Benjamin Cummings

Online
http://www.nature.com/scitable - you need to register but this site is free.
Others as provided below.

THE DETAILED OBJECTIVES
NOTE: There may be some overlap/ duplication between sections within Physiology and Molecular Medicine

1. The Cell
The nucleus
 Define the term ‘chromosome’
 Describe the packaging of DNA from the double helix through to a condensed (mitotic) chromosome
 List the steps in the process of DNA replication and synthesis
 List and briefly describe the functions of the different types of RNA
 Define transcription and briefly describe the steps of the transcription process
 List and briefly explain other roles of DNA
 Define a gene
 Explain how the sequence of nucleotide bases in a gene translates into instructions for amino acid sequences in polypeptides
 Briefly explain the difference between exons and introns
 Briefly explain how genes are controlled
 Define PCR and briefly outline the technique
 Briefly describe the technique used for DNA sequencing
 Briefly describe the techniques and use of Restriction Digests
 Briefly describe what is meant by a Microarray and give a use for this technique using RNA
 Define a karyotype and describe how this is obtained
 Briefly describe how FISH (fluorescent in situ hybridization) is performed and what this technique can be used for.

Resources: The following are useful online resources but the objectives only require fairly basic information so other resources may well be adequate.
 Use Wikipedia for the objectives above as follows:
(1) PCR - in ‘Variations on the basic PCR technique’ only learn Reverse Transcription PCR (RT-PCR)
- leave out ‘History’ and ‘Patent disputes’
(2) DNA sequencing – look up Sanger sequencing and only read to the end of dye-terminator sequencing
(3) DNA Microarray – read to the end of the “principle” section.

**Fluorescent In Situ Hybridisation (FISH)**
go to [http://www.nature.com/scitable/ebooks/cntNm-16570294/contents](http://www.nature.com/scitable/ebooks/cntNm-16570294/contents)
Open unit 2 and find FISH at 2.1. There are 8 pages to open (including references.)

For Karyotypes:
- Go to [http://atlasgeneticsoncology.org/Educ/PolyMecaEng.html](http://atlasgeneticsoncology.org/Educ/PolyMecaEng.html) and read the introductory section entitled “Chromosomes”. Any basic genetic textbook will have information on how karyotypes are made.
- Also use Scitable for this section. [http://www.nature.com/scitable/ebooks/cntNm-16570294/contents](http://www.nature.com/scitable/ebooks/cntNm-16570294/contents)
Go to unit 2: 2.3. There are 5 pages including the references.

**The cytosol and proteins**
- Describe the steps of protein synthesis in the cytosol
- Briefly describe proteins in terms of their structure (primary to quaternary)
- List the differences between fibrous (structural) and globular (functional) proteins
- List the general functions of proteins and give examples of each function in the body
- Describe the process and effects of protein denaturation
- Explain the nature and role of recombinant proteins
*Use Wikipedia for the objective on ‘Recombinant proteins’*
Read to the end of “Expression of recombinant DNA.”

- Describe how damaged or unnecessary proteins are degraded/ destroyed in the cytosol
- List and briefly describe the laboratory techniques commonly used to analyse proteins
*Use Wikipedia for the objectives:*
(1) Western blot - Read all
(2) Gel electrophoresis - Do not read history

**The cell membrane**
- Describe the chemical composition of the plasma membrane and explain how the composition relates to the functions of the membrane
- Describe the nature and functioning of membrane receptors responding to contact signalling, chemical signalling and electrical signalling
- List the types of chemical signal receptors
- Briefly describe the functioning of G protein-linked receptors including the role of second messengers and protein (phosphate) kinase enzymes
- List and briefly describe two laboratory techniques commonly used to analyse surface markers and other cell antigens: flow cytometry and immunohistochemistry

*Use Wikipedia for the objectives:*
(1) Flow cytometry “principle” section only
(2) Immunohistochemistry - just read the introduction

- Briefly describe the 3 types of membrane junctions
- List the roles of cell adhesion molecules
List and briefly describe the types of extracellular materials and their functions

Cell development and death
- Define a stem cell in terms of the fundamental properties of this cell
- Briefly describe the factors that lead to differentiation of cells
- Define apoptosis, briefly describe its causes, and briefly describe the process of cell death up to phagocytosis
- List and briefly describe the phases of the cell life cycle
- Describe the process of cell division: DNA reduplication, mitosis (with its 4 phases) and cytokinesis
- Name the factors which control cell division
- Name the enzymes that enable cells to enter the different phases of mitosis, or inhibit the process

2. The Molecular Basis of Genetics
- Define allele, genotype, phenotype
- Define autosomal chromosomes, sex chromosomes and homologous chromosomes
- Compare mitosis and meiosis with respect to phases, number of divisions, synapses of homologous chromosomes, number of daughter cells and genetic composition of daughter cells
- Briefly describe the following sources of genetic variation:
  - chromosome segregation and independent assortment
  - crossover of homologues and gene recombination
  - random fertilization

Patterns of Mendelian inheritance
- Define ‘dominant allele/ trait’ and ‘recessive allele/ trait’, and give common examples of each
- Define ‘homozygous’ and ‘heterozygous’
- Explain how dominant and recessive inheritance takes place at a genetic level
- Explain the chances that two siblings of heterozygous parents will have the same dominant trait and the same recessive trait
- Define ‘incomplete dominance’ and give an example
- Define ‘codominance’ and give an example
- Explain how sex-linked inheritance takes place at a genetic level, and give examples of common traits inherited in this way
- Explain how polygenetic/ multifactorial inheritance takes place at a genetic level, and give examples of common traits inherited in this way

Epigenetic inheritance
- Briefly explain how epigenetic marks such as methyl or acetyl groups affect the activation and functioning of DNA

Chromosome abnormalities
- Define ‘structural chromosome abnormalities’ and give examples of the clinical conditions and effects they produce
- Define ‘numerical chromosome abnormalities’ and give examples of the clinical conditions and effects they produce

Use Wikipedia for the objectives on ‘Chromosome abnormality’.
http://atlasgeneticsoncology.org/Educ/PolyMecaEng.html has more detail for explanation.
3. The Molecular Basis of Immunology
The strength of the immune system lies in the integration of all its facets so that is how you should study this section. Study the whole chapter related to immunology and the immune system in ‘Human anatomy & physiology’ (Marieb EN, Hoehn K)

Functions of the lymphatic system
List the functions of:
- lymphatic vessels
- lymphocytes
- lymphoid tissues and organs

Nonspecific immune defences
- Define the terms antigen, hapten and antigenic determinant
- Describe the general role of the following in host defenses:
  - physical barriers
  - phagocytes – neutrophils and macrophages
  - natural killer cells
  - chemicals
- With respect to the complement system:
  - List the proteins which make up the system and their functions
  - Describe the activation of the system in the context of the classical and alternate pathways
- Describe the processes that make up the inflammatory response with reference to
  - the cells involved
  - the mediators involved
  - the consequences
  - its termination

Specific immune defences
- Define ‘adaptive immune response’ and list its main features
- List the antigen-presenting cells
- Describe the functions of antigen-presenting cells
- Briefly describe the role of the humoral response (i.e. B-cells and antibody-mediated immunity); in addition:
  - Describe the structure of an antibody.
  - Compare the structures of the 5 classes of antibody and relate these to their specific functions
  - Describe the molecular process by which antibody diversity is generated
  - Briefly outline the cell-mediated immune response
  - Identify and describe the roles of MHC class I and MHC class II molecules
- Describe the role of CD4 T-cells
- Describe the role of CD8 T-cells
- Describe the molecular process by which T-cell receptor diversity is generated
4. The Molecular Basis of Cancer

The information for this section must be obtained from different sources as there is no freely-available resource which has been found to cover all the objectives and the textbook you have been advised to use for anatomy and physiology (Marieb) has only one short section on cancer. It is, however, advisable to read the latter first to set the scene for this section.

The three main resources that it is suggested that you use are:

1. **Molecular Biology of the Cell. Alberts et al**

To access the book online:


This brings you to the PubMed search page.

- Under ‘Search’ use the dropdown menu to find ‘Books’
- Type ‘Molecular biology of the cell’ into the search box and click on ‘Search’

Scroll down to find the book by Alberts et al. Click on the icon. This brings you to the homepage for the book.

You now want to get access to the whole of Chapter 23 ‘Cancer’ in the book. There are 5 sections in this chapter. They are:
- Cancer as a Micro-evolutionary Process
- The Preventable Causes of Cancer
- Finding the Cancer-Critical Genes
- The Molecular Basis of Cancer-Cell Behavior
- Cancer Treatment: Present and Future

To find each of these sections, type its name into the search box on the book’s homepage and click on ‘Go’. This brings you to that section.

2. **Wikipedia.** There is an entry on Cancer and it has numerous links to the various subsections/objectives. Use these as necessary to cover the objectives below. Where possible, there is an indication of which extra link to use next to the objectives.

3. **YouTube: Oncology for Medical Students**

   This is an excellent series of videos:

   - **Cancer Biology**
     a) Neoplasia part 1: definition, how it relates to cancer
     b) Neoplasia part 2: Differences between benign and malignant neoplasms
     c) 3: Molecular basis of cancer part 1: changes in DNA underlie cancer
     d) Hallmarks of Cancer (part 1)
     e) Hallmarks of cancer (part 2)
     f) Tumour Suppressor Genes (Retinoblastoma and the two hit hypothesis, p53)
     g) Proto-oncogenes and Oncogenes
     h) Clonal Selection
     i) Clinical features of cancer: how cancers cause clinical symptoms
4. **General pathology textbooks.** If you have access to any general pathology textbooks, they usually have a chapter on cancer which should have much of the information you require. No particular textbook has been identified as not all candidates have access to such a resource.
<table>
<thead>
<tr>
<th>Topic</th>
<th>Previous learning in Molecular Medicine</th>
<th>Possible resources – note that this does not exclude the use of the other resources listed or that you may find.</th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction to cancer</td>
<td>Genetics</td>
<td>Molecular Biology of the Cell Wikipedia: Cancer The hallmarks of cancer Oncology for Medical Students: Hallmarks: <a href="https://www.youtube.com/watch?v=ea-CALIn7hA">https://www.youtube.com/watch?v=ea-CALIn7hA</a> <a href="https://www.youtube.com/watch?v=zSDOZw72BU">https://www.youtube.com/watch?v=zSDOZw72BU</a></td>
<td>The student should: 1. Recognise that cancer is a significant cause of morbidity and mortality (disease and death) 2. Describe the differences between benign and malignant tumours 3. Describe the gross patterns of cancer growth 4. Describe the 2 pathways of carcinoma growth and progression 5. Explain the concept of “differentiation” and “dedifferentiation” as applied to cancer 6. Explain why cancer takes time to develop 7. Explain why cancer is a disease of the genome 8. Explain the development of cancer in terms of increasing numbers of mutations and epigenetic changes, and define “genetic instability” 9. Outline the major “hallmarks” of cancer as defined by Hanahan and Weinberg (Cell, 2011, 144:5 p646 -674) Note: you do not need to read the original paper but you must know that there are 8 of them, not 6 as in the original (2000) paper 10. Describe the 2 “enabling characteristics” of cancer. Hanahan and Weinberg (Cell, 2011, 144:5 p646 -674)</td>
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<tr>
<td>Oncogenes and Tumour Suppressor Genes</td>
<td>Cell signalling pathways, Cell death,</td>
<td>Oncology for Medical Students Molecular Biology of the Cell</td>
<td>1. Define proto oncogene and oncogene 2. List the classes of proto-oncogenes. 3. Explain the functions of proto-oncogenic proteins and give an example of each. 4. Describe how proto-oncogenes are converted to oncogenes 5. Explain how this conversion leads to over-activation or over-expression of the encoded protein 6. Define tumour suppressor gene 7. Describe the recessive nature of tumour suppressor genes 8. Explain why germline mutations of tumour suppressor genes are possible and how they lead to increased cancer susceptibility 9. Explain the Knudson two hit hypothesis 10. Explain how anti-apoptotic protein (e.g. BCL2) up-regulation prevents apoptosis</td>
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<td>Cell Cycle: Tumour Suppressor Genes and Oncogenes</td>
<td>Cell cycle and mitosis, Cell death</td>
<td>Oncology for Medical Students Molecular Biology of the Cell</td>
<td>1. Name two oncoproteins in the cell cycle 2. Name two tumour suppressors which play an important role in regulating the cell cycle 3. Describe how progression from G1 to S is regulated with particular reference to Rb 4. Describe the functions of p53 in regulating the cell cycle, apoptosis, DNA repair and angiogenesis.</td>
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<td>Immortalisation of tumour cells</td>
<td></td>
<td>Oncology for Medical Students Molecular Biology of the Cell</td>
<td>1. Define cell senescence and immortality. 2. Explain why telomere shortening leads to replicative senescence 3. Describe how cells become immortal</td>
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<td>Angiogenesis</td>
<td></td>
<td><a href="https://www.youtube.com/watch?v=f4SgXw2GxO0">https://www.youtube.com/watch?v=f4SgXw2GxO0</a> <a href="https://www.youtube.com/watch?v=Qu2DVcxCLCs">https://www.youtube.com/watch?v=Qu2DVcxCLCs</a></td>
<td>1. Outline the process of angiogenesis 2. Explain how cancer cells induce angiogenesis 3. Describe how tumour vasculature differs from normal vasculature at the macro and micro level 4. Explain how tumour angiogenesis could be a target for treatment of cancer</td>
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<td>Invasion and metastasis</td>
<td></td>
<td>Molecular Biology of the Cell Oncology for Medical Students</td>
<td>1. Define “invasion” and “metastasis” 2. Give 4 routes of metastasis 3. Describe the necessary steps tumours must undergo in each of these forms of metastasis 4. List the multiple sequential steps of the metastatic cascade 5. Define and describe the role of the epithelial to mesenchymal transition in metastasis</td>
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<td>Topics</td>
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| Concepts of the micro-environment and cancer stem cells | Molecular Biology of the Cell | 1. List the components of the tumour microenvironment  
2. Describe how the microenvironment affects tumour growth and metastasis  
3. Define the function of a cancer stem cell |
2. Hypothesise why this difference occurs  
3. Explain how this difference is utilized to detect cancers by PET scans |
| Epigenetics in cancer | Genetics | 1. Define epigenetics.  
2. Describe the major epigenetic mechanisms.  
3. Briefly explain how the epigenetic mechanisms modify gene transcription.  
4. Discuss ways in which epigenetic abnormalities may contribute to carcinogenesis |
| Inherited tumour syndromes | Genetics | 1. Distinguish between acquired (somatic) and inherited (familial) cancer at the genetic level  
2. Describe the association between Rb and retinoblastoma.  
3. Describe the association between BRCA mutations and cancer |
| Aetiological agents in cancer – toxins | Molecular Biology of the Cell: Carcinogen | 1. Explain the differences between tumour initiators and promoters  
2. Explain what is meant by a procarcinogen and why activation varies in different individuals |
| Aetiological agents in cancer – viruses | Wikipedia: Oncovirus, Wikipedia: Infectious causes of cancer | 1. Explain DNA virus oncogenesis and the role of P53 and Rb inactivation, e.g. by HPV  
2. Outline oncogenesis by RNA viruses  
3. List the common viruses which cause cancer and the specific types of cancer they cause. |
| Aetiological agents in cancer – Radiation | Wikipedia: Carcinogen | 1. Describe the mechanism by which radiation causes cancer  
2. List the most important sources of radiation for humans |
| Aetiological agents in cancer – Inflammation and infections | Immunology | 1. Describe the role played by the immune system in the initiation and maintenance of cancer.  
2. Describe the role played by H. pylori in gastric cancer as an example of host-organism interaction.  
3. Outline some possible roles of infection in other cancers. |
| Cancer therapy | Molecular Biology of the Cell: Chemotherapy | 1. Outline the chemotherapy mechanisms which target dividing cells  
2. Define what is meant by “broad spectrum” therapy as opposed to “targeted” therapy  
3. Explain why and how angiogenesis can be a target for anticancer therapy |
| Why cancer therapy fails | Wikipedia: Antineoplastic resistance | Explain the host and host-tumour factors which lead to failure of chemotherapy  
Explain how individual tumor genetic variation contributes to resistance  
Explain the mechanism of drug efflux as a cause of resistance and the strategies used to counter this  
Explain why the cancer stem cell contributes to resistance |
5. The Molecular Basis of Infectious Disease

Objectives for Infectious Diseases

- The objectives for this section are covered in the following textbook, available online through the Pub Med bookshelf.
- The relevant chapter is given next to the headings.
  - Please note: This textbook provides a very useful summary at the beginning of each chapter and it is strongly recommended that you begin with this summary.
  - It is also suggested that you follow the objectives closely as there is more information than required in some sections in this textbook.

Structure of bacteria (Chapter 2)

- Define what is meant by the terms “coccus” and “bacillus”
- Describe the different cell arrangements found in cocci
- Describe the different shapes of bacilli
- The nucleoid:
  - Describe the general structure/shape of a bacterial chromosome
  - Compare a bacterial nucleoid and chromosome structure with a mammalian cell nucleus and chromosome structure
- Surface appendages:
  - Compare the structure and function of flagellae and pili
- Surface layers:
  - Explain what is meant by the terms “Gram positive” and “Gram negative” and how these different staining patterns arise
  - Compare and contrast the surface layers of Gram positive and Gram negative bacteria
  - Describe the structure and basic steps in the synthesis of peptidoglycan.
  - Describe the basic structure of lipopolysaccharide/endotoxin (detail for different bacteria not required)
  - State which types of bacteria contain lipopolysaccharide
  - Describe the outer membrane of Gram negative bacteria.
  - Explain what is meant by the periplasmic space of Gram negative bacteria
  - State which types of bacteria contain techoic acid
  - Define what is meant by “mesosomes”.

Bacterial genetics (Chapter 5)

- Compare binary fission in bacteria with mitosis in mammals
- The bacterial genome:
  - Describe a typical bacterial chromosome.
  - Define the term “plasmid”
  - Discuss the role of plasmids in human diseases caused by bacteria
  - Define the term “bacteriophage”
  - Describe the differences between virulent and temperate bacteriophages
- Exchange of genetic information:
  - Describe the process of transformation in bacteria
  - Describe the process of transduction with respect to bacteria
  - Briefly outline the process of conjugation in bacteria
  - Explain how the above processes contribute to genetic variation in bacteria.
**Bacterial pathogenesis (Chapter 7)**
- Define “host susceptibility” and “host resistance”
- Relate the above concepts to the immune system in humans.
- Describe how the host response can cause disease.
- Describe the adaptations necessary for bacteria to live within mammalian cells
- Define “virulence”
- Define and describe each of the following factors involved in virulence:
  a. Adherence and colonisation factors
  b. Invasion factors
  c. Capsules
  d. Endotoxin
  e. Exotoxins
  f. Siderophores

**Antimicrobial chemotherapy (Chapter 11)**
- For each of the following different types of antimicrobial agent, list the major examples and describe the mechanism:
  - Inhibition of bacterial wall synthesis
  - Disruption of (a) bacterial membranes and (b) fungal membranes
  - Inhibition of nucleic acid synthesis:
    i) Interference with nucleotide synthesis
    ii) Impairment of template function of DNA
    iii) Inhibition of DNA-directed DNA polymerase
    iv) Inhibition of DNA replication
    v) Inhibition of ribosome function
    vi) Inhibition of folate metabolism
- For each of the following, describe the mechanism of resistance to antimicrobial chemotherapy:
  - Resistance due to altered receptors (β Lactam, vancomycin, macrolide-lincomycin, rifampin, sulphonamide trimethoprim, quinolone)
  - Resistance due to decreased drug entry (tetracycline, aminoglycoside)
  - Resistance due to destruction or inactivation (β Lactam)
  - Synthesis of resistant metabolic pathways (concept only)

**Structure and classification of viruses (Chapter 41)**
- Define and describe what is meant by the term “virus”
- Describe the structure of a virus in terms of the nucleic acid, capsid and envelope
- Describe the morphological classification of viruses
- Describe the different arrangements of the genome in RNA viruses
- Describe the different arrangements of the genome in DNA viruses

**Human immunodeficiency virus (Chapter 62)**
- Relate the levels of virus and the function of the immune system in the different phases of disease caused by HIV
- Name the cells infected by HIV
- Define “opportunistic infection” and explain why this occurs in HIV infection
- Define “AIDS”
- Briefly describe the structure of HIV
- Explain the function of reverse transcriptase
- Describe the process of HIV replication from attachment of the virus to the budding of new virions
- Outline the pathogenesis of disease caused by HIV
- Describe how HIV infection is diagnosed by means of a) antibodies and b) PCR
- Describe the strategies used to control and prevent HIV infection

**Malaria (Chapter 83)**
- Describe the stages of the malaria paroxysm
- Describe and explain the periodicity of fever in malaria
- List the 4 species of Plasmodium responsible for most cases of malaria
- Name the vector of malaria
- Describe the lifecycle of malaria, highlighting the difference between Pl. falciparum and the other species
- Describe the pathogenesis of malaria
- Describe the host defences against malaria
- Outline the epidemiology of malaria