

# MCAT: Biochemistry Webinar Session Handout

## Content Quiz

1) Enzyme B is introduced to a reaction for which the reactants are substrates to enzyme B. Which of the following will occur?

- A. The forward and reverse reactions will proceed slower.
- B.  $K_{eq}$  for the reaction will increase.
- C. The rate at which the equilibrium is reached is decreased.
- D. The rate at which the equilibrium is reached is increased.

2) Which of the following will NOT be oxidized in the presence of  $KMnO_4$ ?

- A. t-butyl alcohol
- B. Heptanol
- C. 2-propanol alcohol
- D. *cis*-2-pentene

3) The carbonyl carbon is very:

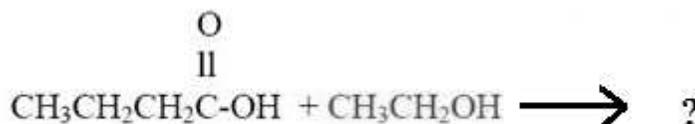
- A. electrophilic.
- B. nucleophilic.
- C. acidic.
- D. basic.

4) Rank the following molecules in order of increasing acidity.

- I.  $CH_3CH_3CH_2ClCOOH$
- II.  $CH_2ClCH_3CH_3COOH$
- III.  $CH_3CH_3CH_2FCOOH$

- A.  $III < II < I$
- B.  $II < III < I$
- C.  $I < II < III$
- D.  $II < I < III$

5) What is the most likely product of the following reaction?

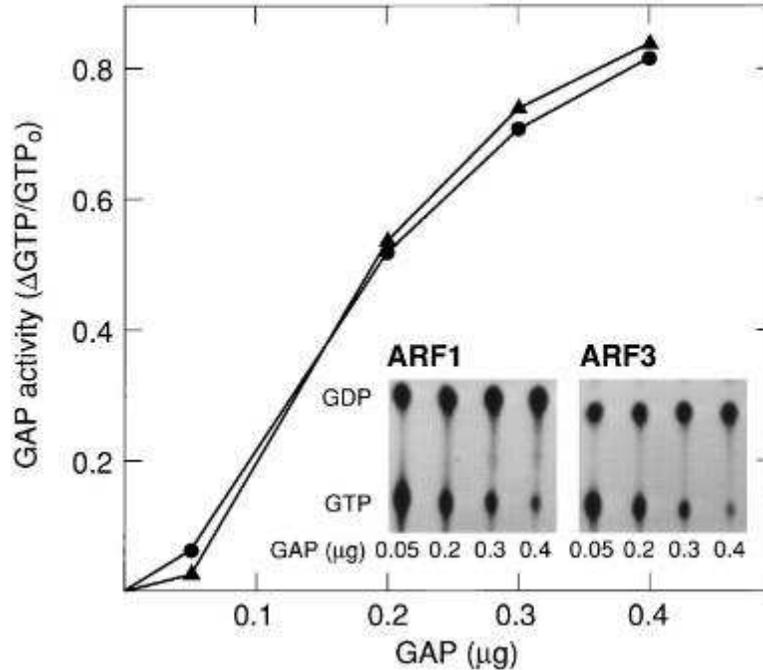


- A. Ethyl butanamide
- B. Hexanoic acid
- C. Ethyl butanoate
- D. 1-ethyl propanoic acid

### **Practice Passage 1**

Owing to its large size, the Golgi apparatus (GC) was one of the first organelles to be discovered and observed in detail. Cells synthesize a large number of different macromolecules. The Golgi apparatus is integral in modifying, sorting, and packaging these macromolecules for cell secretion or use within the cell. It is essential to the compartmentalized eukaryotic cell. Pharmaceuticals that interrupt the efficiency of the Golgi apparatus reduce cell viability and can serve as valuable cancer treatments.

ADP-ribosylation factor 3 (Arf3) is responsible for the recruitment of cytosolic coat protein complexes (COPs) and subsequent retrograde transport from the Golgi apparatus. Arf3 is activated by guanine nucleotide exchange factors, which substitutes guanosine triphosphate (GTP) for guanosine diphosphate (GDP). Upon GTP substitution, Arf3 is rearranged and releases the N-terminus of the polypeptide chain from a site in the protein and instigates their sequestration to phospholipid bilayers. Through its coupling with a bilayer, Arf3 further facilitates vesicle formation by the recruitment of the coatomer protein complex COP-1 (subunits are represented by  $\beta\gamma\delta\zeta$ ). The Arf3 GTPase activating protein catalyzes the conversion of Arf3-bound GTP to GDP, inactivating the protein. GTPase activity is increased by Arf3 binding to COP-1. Assays were performed to determine GTPase activity as a function of GTPase activating protein (GAP) present. In addition phosphorimages of protein-bound  $[\alpha\text{-}^{32}\text{P}]$  and  $[\alpha\text{-}^{32}\text{P}]$  GTP from incubations with the indicated amounts of ARF GAP in this experiment were performed with the results shown in figure 1.



**Figure 1** GAP-stimulated GTPase activity of native ARF1 and ARF3. GTPase activity of ARF1 (•) and ARF3 (▲) each 0.15 mM, with the indicated amount of purified GAP, was determined using assay. Angiogenesis, the formation of new blood vessels, is an essential step for cancer progression. This formation is inhibited in part by the mechanism of monensin A, an inhibitor of protein transport from the endoplasmic reticulum to the Golgi apparatus. Monensin A has been shown to reduce Arf3-driven cell surface vascular endothelial growth factor receptor (VEGFR) expression on endothelial cells in culture, resulting in reversible interruption of the Golgi apparatus and partial remission *in vitro*. Due in part to low tissue uptake, monensin A is not an effective anti-cancer agent; but, it has led to the recognition of deoxymannojirimycin (DMNJ) as a promising cancer therapeutic.

DMNJ is hypothesized to attach to a protein—protein contact interface of Arf3, preventing GTP exchange by GEF and disrupting Arf3 membrane localization in the initial critical step of COP1 recruitment and vesicle formation. In clinical settings, treatment with DMNJ has led to remission in rat models of skin cancer.

6) The gene products that are packaged in Arf3 -COP vesicles are most likely destined for:

- A) the smooth endoplasmic reticulum.
- B) the rough endoplasmic reticulum.
- C) the lysosomes.
- D) the nucleolus.

7) Which of the following is the likely outcome of hydrolysis of a  $\zeta$  phosphate group from an Arf3-bound GTP?

- A) Loss of primary protein structure
- B) Protein-membrane binding
- D) Protein activation
- D) Protein inactivation

8) Which of the following enzymes performs a similar function to the Arf3 GTPase activating protein?

- A) Pyruvate Kinase
- B) Lactate dehydrogenase
- C) Alkaline phosphatase
- D) Peptidyl transferase

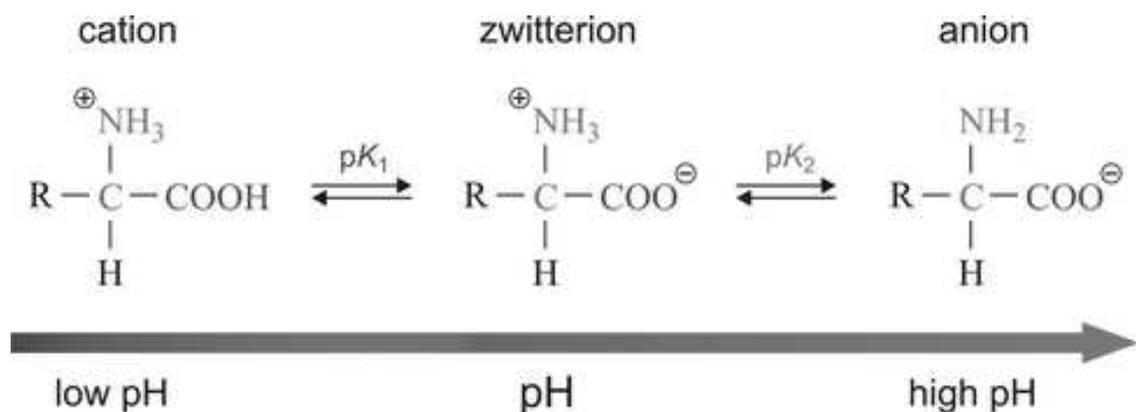
9) The mechanism of Monensin A described in the passage indicates that the drug would be best used to treat:

- A) bacterial infection by *Bacillus anthracis*.
- B) viral infection by *Varicella zoster*.
- C) bacterial infection by *Salmonella enterica*.
- D) fungal infection by *Candida albicans*.

10) GTP is classified as a member of which class of biological molecules?

- A) Amino acids
- B) Peptides
- C) Nucleotides
- D) Nucleic Acids

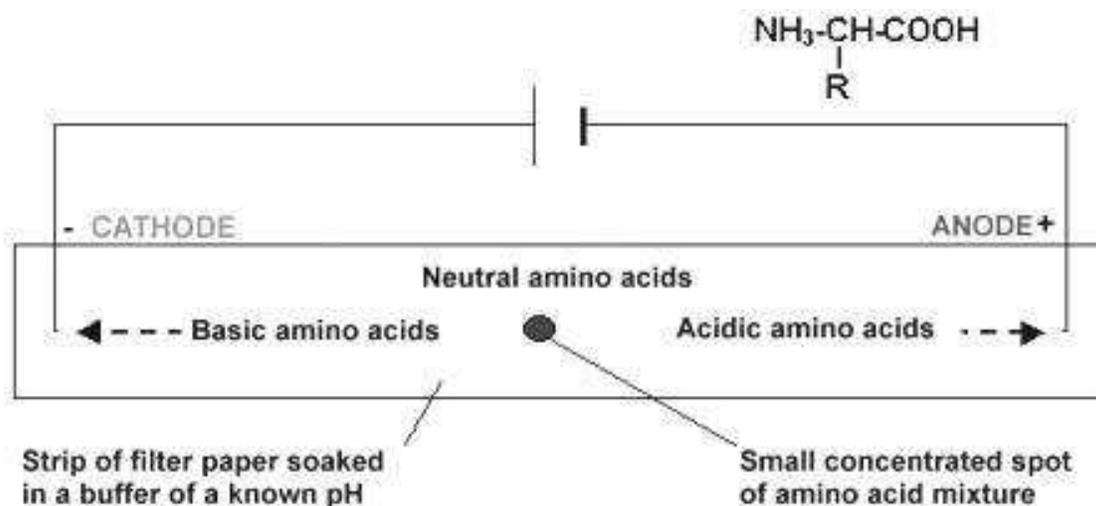
## Amino Acids



When  $\text{pH} > \text{pK}_a$  the \_\_\_\_\_ form predominates.

When  $\text{pH} < \text{pK}_a$  the \_\_\_\_\_ form predominates.

When  $\text{pH} = \text{pK}_a$  the \_\_\_\_\_ form predominates.



When placed into an electrophoretic gel at a  $\text{pH} = 8$ , to which node will the following amino acids migrate?

- (i) Ala      (ii) Pro      (iii) Glu      (iv) Arg

**Protein Structure**

Level	Description	Stabilized by	Example
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Primary			
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Secondary			
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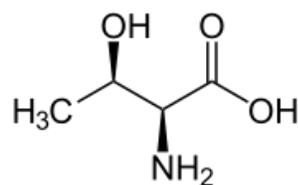
Tertiary			
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Quaternary			
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11) One of the problems in certain forms of Schizophrenia is a loss-of-function mutation to peptidyl transferase. What process is most likely to be halted in these patients?

- A. Binding of the mRNA template to the ribosome
- B. Construction of the cellular ribosome
- C. Construction of the primary structure of neuroproteins
- D. tRNA recognition of mRNA codons.

12) A polar-substrate binding enzyme is most likely to have threonine residues richly populating which region? :



- A. The interior of the enzyme.
- B. The exterior of the enzyme.
- C. The active site of the enzyme.
- D. Within an alpha-helical structure.

## **Build your Science Foundation**

### **Non-Polar AA**

### **Aromatic AA**

### **Polar + Charged**

### **Polar – Charged**

### **Polar Uncharged**

## **Where are we Likely to find each on a protein?**

You should prioritize you AA studying as follows in order to maximize efficiency and points on test day:

1. Full name and side group chemical behavior
2. 3 letter abbreviation
3. 1 letter abbreviation

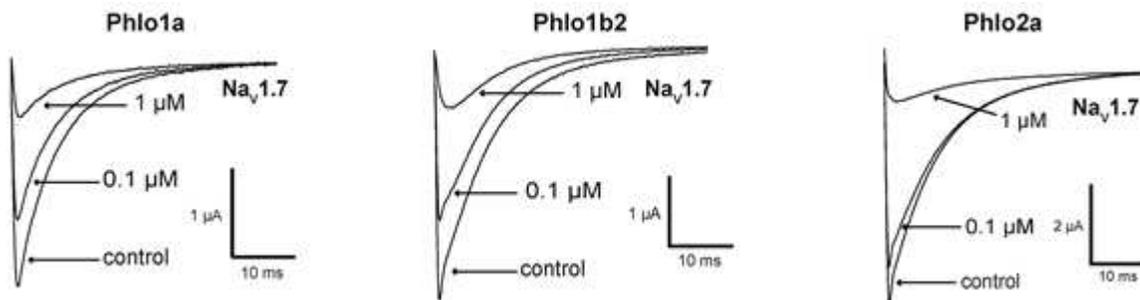
## 4. Side chain structure

**Practice Passage 2**

Voltage-gated sodium ( $\text{Nav}$ ) channels are responsible for propagating action potentials. Humans contain a complex repertoire of nine  $\text{Nav}$  channel subtypes denoted  $\text{Nav}1.1$ – $\text{Nav}1.9$ .  $\text{Nav}1.7$  plays a crucial role in the human pain signaling pathway and it is an important therapeutic target for treatment of chronic pain.

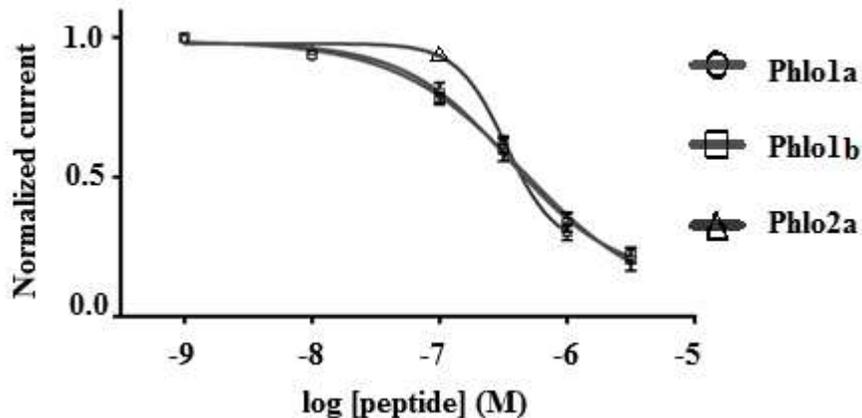
A scientist sought to determine the diversity of  $\text{Nav}1.7$ -active peptides in the venom of an Australian tarantula and to characterize their potency and subtype selectivity. Three tarantula peptides were reduced and alkylated using the volatile reagent triethyl-phosphine, prior to tryptic digestion. The mass of each peptide was found to increase by 270 Da following reduction/alkylation.

Next the three peptides were isolated. TRTX-Phlo1a, -Phlo1b and -Phlo2a, inhibit human  $\text{Nav}1.7$  ( $\text{hNav}1.7$ ). Phlo1a and Phlo1b are 35-residue peptides that differ by their C-terminal amino acid. The partial sequence of Phlo2a revealed extensive positively charged residues *in vitro*. Human oocytes were treated with each peptide and  $\text{IC}_{50}$  (how much of a particular substance is needed to inhibit a given biological process by half) and  $V_{0.5}$  (the voltage at which the channels are half-maximally activated) was measured for each of the peptides. Phlo1a and Phlo1b inhibit  $\text{hNav}1.7$  with  $\text{IC}_{50}$  values (mean  $\pm$  S.E.M) of  $439 \pm 46$  and  $400 \pm 61$  nM, respectively, with only minor activity on  $\text{hNav}1.5$ . Although similarly potent at  $\text{hNav}1.7$  ( $\text{IC}_{50}$   $333 \pm 19$  nM), Phlo2a also potently inhibited  $\text{hNav}1.2$  and  $\text{hNav}1.5$ .



**Figure 1** Effects of venom peptides on  $\text{hNav}1.7$  expressed in oocytes

Whole-cell Na current traces were made on all three peptides in the absence and presence of 0.1 or 1  $\mu\text{M}$  peptide (figure 1). Sodium currents were evoked by a 50-ms step depolarization to 0 mV from a holding potential of  $-80$  mV every 10 s. Mean  $V_{0.5}$  for the  $\text{Nav}1.7$  channel was observed to shift from  $-18$  mV to  $-12$  mV and  $-8$  mV. Concentration-effect curves for inhibition of  $\text{hNav}1.7$  by Phlo1a, Phlo1b and Phlo2a ( $n = 15$ ) were recorded as well (figure 2).



**Figure 2** Concentration-effect curves for inhibition of  $\text{hNav}1.7$

The majority of tarantula-venom peptides are 3.0–4.5 kDa in size and highly disulfide-bridged. These bridges allow them to form a highly stable knot fold that provides resistance to chemical and thermal degradation as

well as proteases. Numerous spider venom peptides have been shown to modulate the activity of Nav channels and these peptides represent a rich source of research tools and therapeutic lead molecules.

- 13) What is the effect of the spider-venom peptides on channel activity?
- A. All three peptides inactivate the S4 helix in hNav1.7 channels.
  - B. All three peptides cause a depolarizing shift in the voltage-dependence of hNav1.7 activation.
  - C. All three peptides cause a hyperpolarizing shift in the voltage-dependence of hNav1.7 activation.
  - D. All three peptides cause the cell membrane to transition from resting to polarized.
- 14) A central aspect of developing new anesthetics is the specificity of the agent's signaling. Based on the data from the experiment, which of the peptides would be LEAST effective as an anesthetic?
- A. Phlo1a
  - B. Phlo2b
  - C. Phlo2a
  - D. Phlo1b
- 15) Which of the following would best explain the reason for the variance observed in channel effect by the peptides studied?
- A. Phlo1a has a significantly lower molecular weight than the Phlo2a and Phlo1b peptides.
  - B. Phlo2a has a lower  $IC_{50}$  compared to Phlo1a and Phlo1b.
  - C. C-terminal residues influence Nav subtype selectivity of venom peptides.
  - D. Phlo2a binds to the channel at multiple sites with positive cooperativity.
- 16) Which amino acid is most likely to be found protecting the receptor binding areas on the venom peptides discussed in the passage?
- A. M
  - B. H
  - C. C
  - D. W
- 17) Nodes of Ranvier act as relays for myelinated neuron signaling. How might the action potentials of such a neuron be affected if the intermodal distances were increased significantly?
- A. Action potentials might fail to traverse the axon.
  - B. Action potentials might travel slower than their normal velocity.
  - C. Action potentials would travel faster than their normal velocity.
  - D. Action potentials would remain unaffected due to the all-or-nothing response.



## Enzymes and Enzymatic Regulation

Michaelis-Menten Equation:

$$v = V_{\max}[S] / (K_m + [S])$$

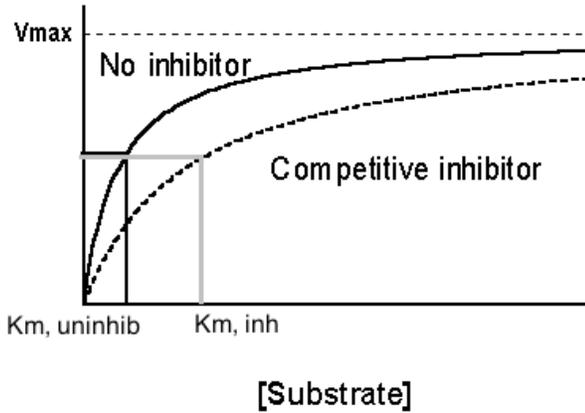
$K_m = [S]$  when the reaction is at  $1/2 V_{\max}$

Reciprocal Michaelis-Menten:

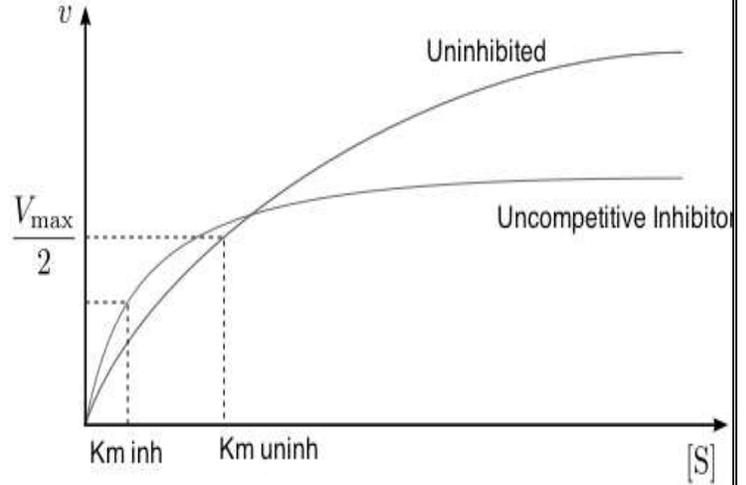
$$1/v = (K_m / V_{\max}[S]) + (1/V_{\max})$$

Competitive Inhibitor:

- Binds to active site
- Competes for active site

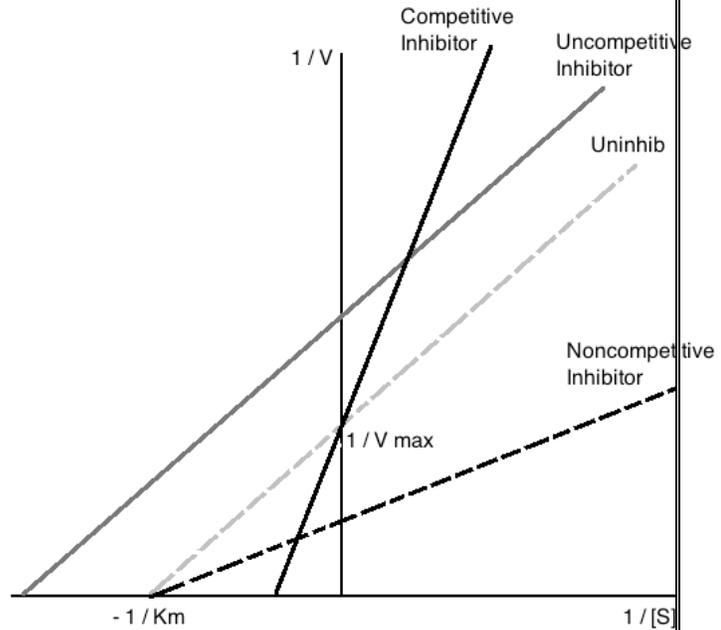


- Bind to enzyme substrate complex
- Binds at allosteric site



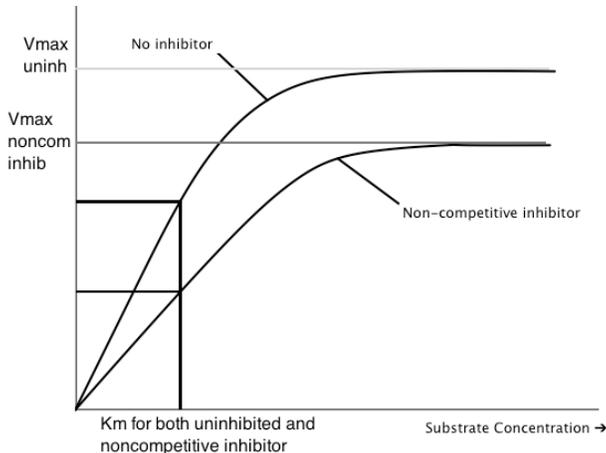
Lineweaver-Burk Plot:

- Reciprocal of  $v$  and  $[S]$
- X intercept is  $-1 / K_m$
- Y intercept is  $1 / V_{\max}$



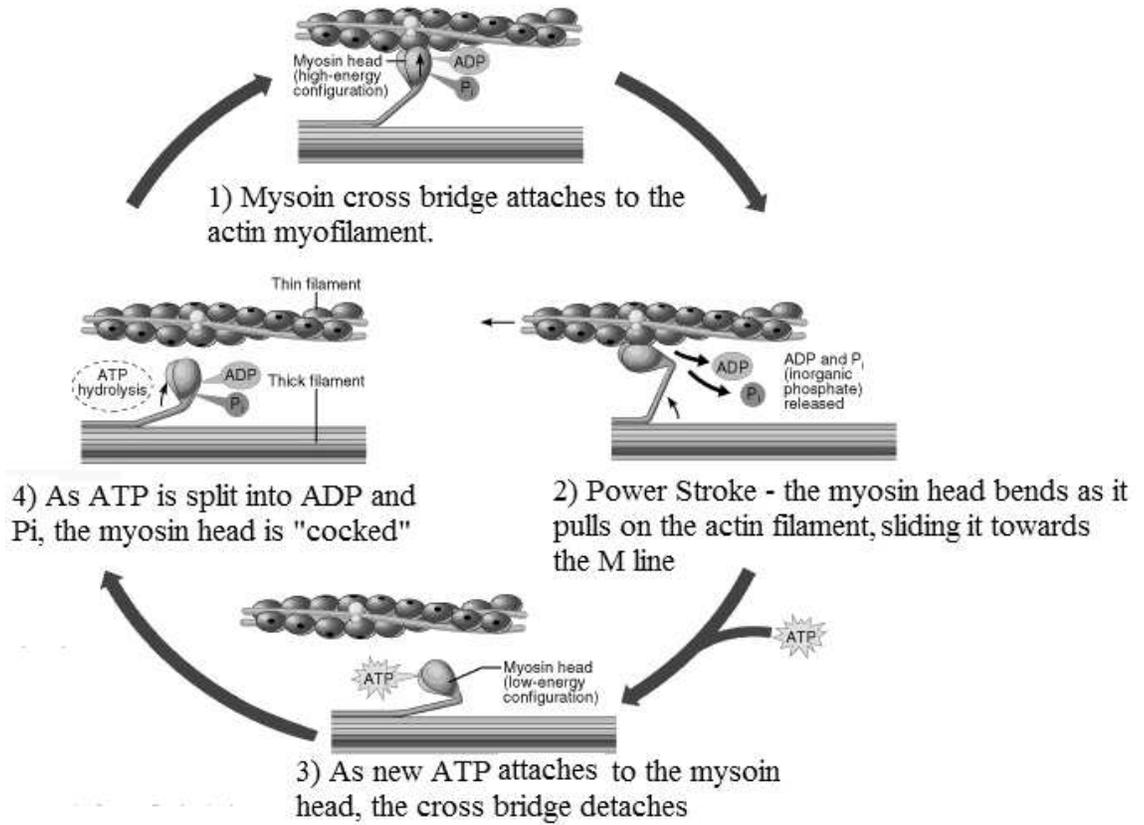
Noncompetitive Inhibitor:

- Binds to allosteric site
- Changes 3° structure of active site

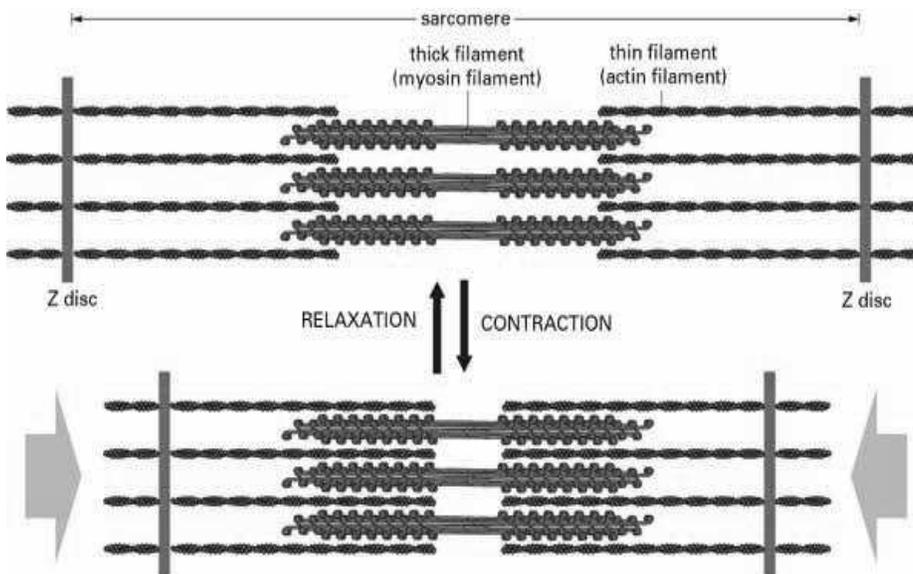


Uncompetitive Inhibitor:

# Motor Proteins



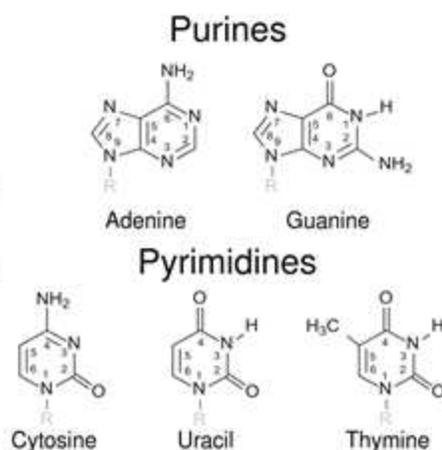
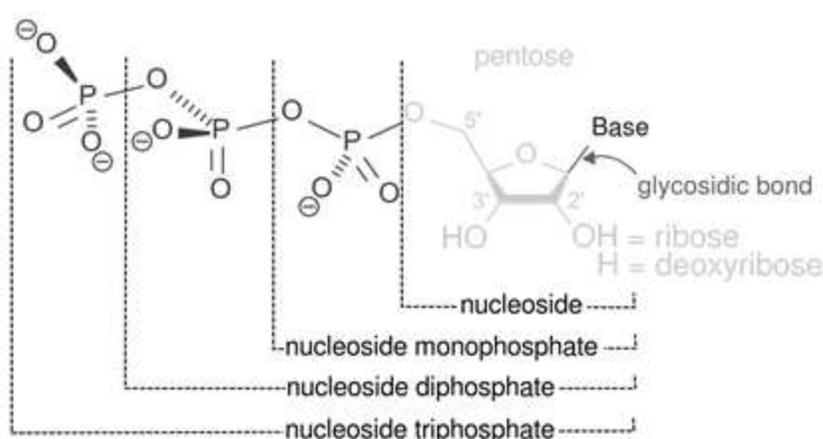
# Sarcomere

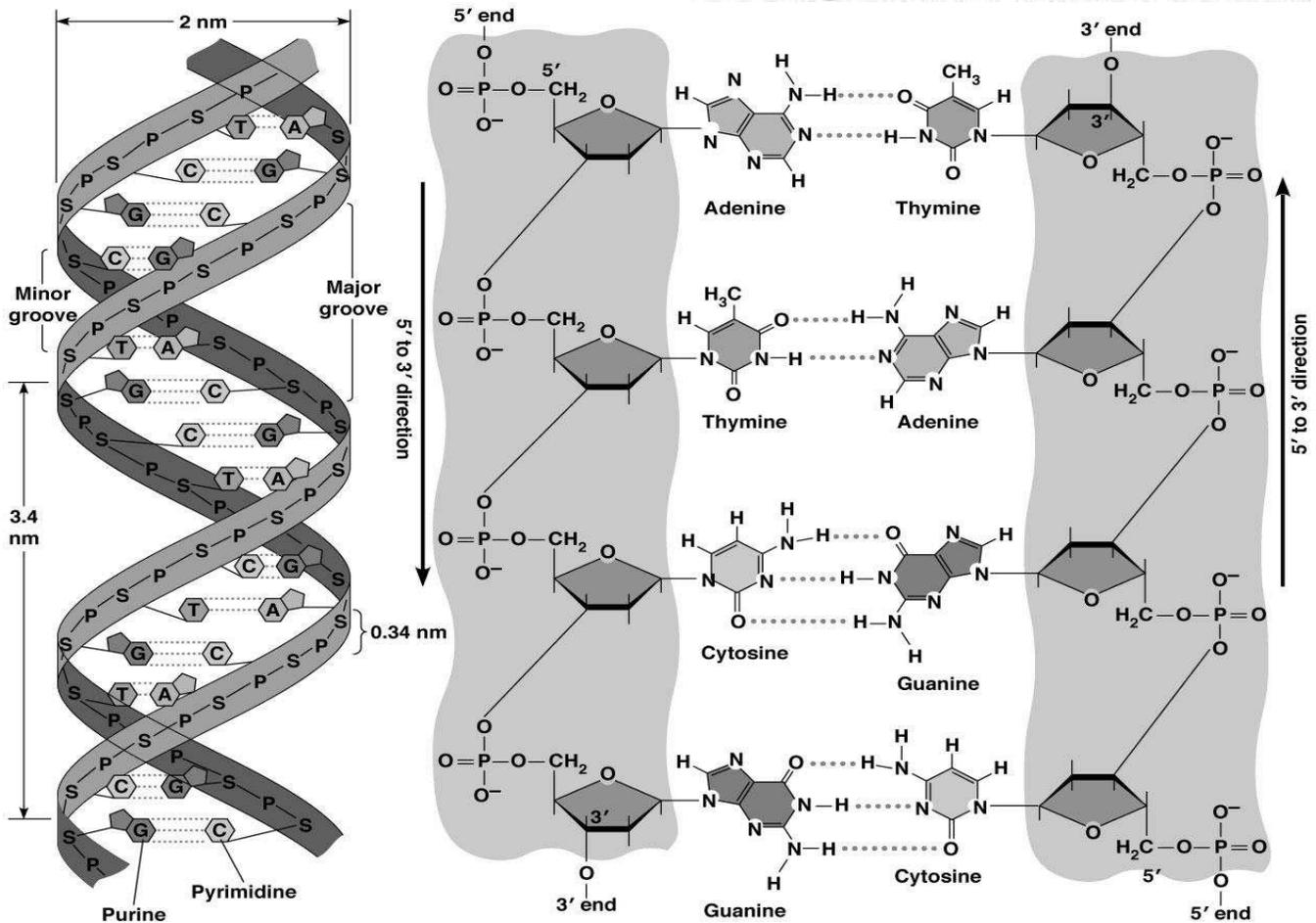


## Nucleic Acids

### Nucleotide Functions:

1. Energy stores for future use in phosphate transfer reactions. These reactions are predominantly carried out by ATP.
2. Forming a portion of several important coenzymes such as NAD<sup>+</sup>, NADP<sup>+</sup>, FAD and coenzyme A.
3. Mediators of cellular processes such as second messengers in signal transduction events. The predominant second messenger is cyclic-AMP (cAMP), a cyclic derivative of AMP formed from ATP.
4. Neurotransmitters and signal receptor ligands. Adenosine can function as an inhibitory neurotransmitter, while ATP also affects synaptic neurotransmission throughout the CNS and PNS. ADP is an important activator of platelet functions resulting in control of blood coagulation.
5. Controlling numerous enzymatic reactions through allosteric effects on enzyme activity.
6. Activated intermediates in numerous biosynthetic reactions. For example S-adenosylmethionine is involved in CH<sub>3</sub> transfer reactions as well as sugar coupled nucleotides involved in glycogen and glycoprotein synthesis.

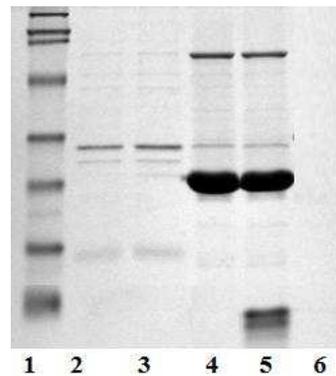




18) Part of the PCR process involves heating up the DNA prior to the addition of RNA primers. A point is reached at which the DNA molecules exist as single strands. Which of the following DNA sequences will require the highest temperature to achieve this?

- A. 5'-ATTCTGCTATTA-3'
- B. 5'-ATGCUUUTATTA-3'
- C. 5'-GTTCTGCTATTA-3'
- D. 5'-ACGCCTGCTAGC-3'

19) Agarose gel electrophoresis is performed on DNA obtained after an experiment run on portions of gene A. If lanes 4 and 5 used the same protocol, which of the following best explains the additional band in lane 5?



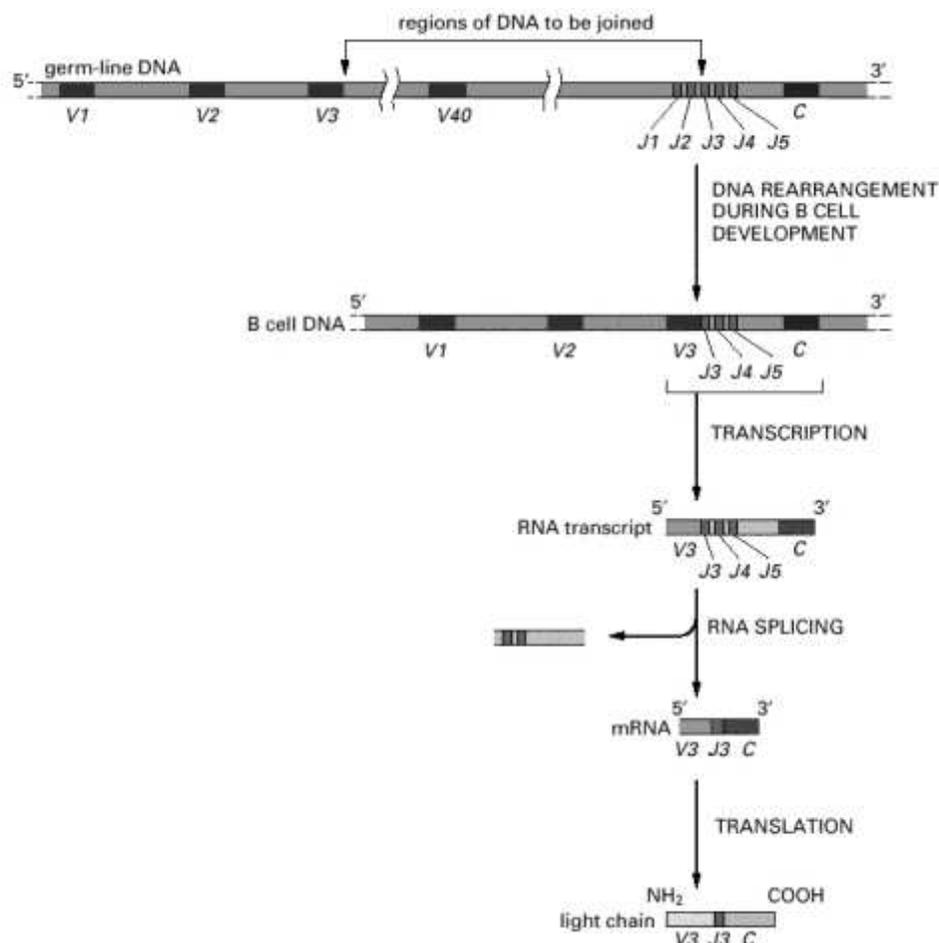
Lane 1 is a ladder of DNA fragments from 50 to 400 bp in length.

- A. The sample in lane 5 was contaminated with DNases.
- B. DNA primers used hybridized to each other and were amplified, generating larger fragments along with the desired fragment.
- C. The sample in lane 5 was contaminated with genomic DNA.
- D. Preparation of the sample for lane 4 mistakenly forgot to remove an intron.

## Practice Passage 3

The variety of human antibodies, over  $10^{12}$  different molecules, poses a unique genetic problem: how can a human, whose genome contains fewer than 50,000 genes, make more antibodies than there are genes in its genome? The mammalian immune system has evolved unique genetic mechanisms that enable it to generate an enormous number of different antibodies by joining separate gene segments together before they are transcribed.

Antibodies are produced from three pools of gene segments and exons. In each pool, separate gene segments that code for different parts of the variable region of the light or heavy chains are brought together by site-specific recombination during B cell development. The combinatorial joining of these segments, called *combinatorial diversification*, greatly increases this variety. Light-chain pools contain one or more constant- (C-) region exons and sets of variable (V) and joining (J) gene segments. The heavy-chain pool contains sets of C-region exons and sets of V, diversity (D), and J gene segments. A  $V_L$  gene segment recombines with a  $J_L$  gene segment to produce a DNA sequence coding for the V region of a light chain, and a  $V_H$  gene segment recombines with a D and a  $J_H$  gene segment to produce a DNA sequence coding for the V region of a heavy chain. Each of the assembled V-region coding sequences is then co-transcribed with the appropriate C-region sequence to produce an RNA molecule that codes for the complete polypeptide chain. The light chain portion of this synthesis is shown in figure 1.



**Figure 1** The V-J-C joining process involved in making a human light chain

In the “germ-line” DNA the cluster of five *J* gene segments is separated from the *C*-region exon by a short intron and from the 40 *V* gene segments by thousands of nucleotide pairs. During the development of a B cell, the randomly chosen *V* gene segment is moved to lie precisely next to one of the *J* gene segments. The extra *J* gene segments and the intron sequence are transcribed (along with the joined *V3* and *J3* gene segments and the *C*-region exon) and then removed by RNA splicing to generate mRNA in which the chosen *V*, *J*, and *C* sequences are contiguous. These mRNAs are then translated into light chains. A *J* gene segment encodes the C-terminal 15 amino acids of the V region, and the *V*-*J* segment junction coincides with the third hypervariable region of the light chain, which is the most variable part of the V region.

Because the antigen-binding site is formed where the hypervariable loops of the  $V_L$  and  $V_H$  come together, the heavy and light chains can pair to form millions of different antigen-binding sites. This number is greatly increased by the loss and gain of nucleotides at the site of gene-segment joining, as well as by somatic mutations that occur with very high frequency in the assembled V-region coding sequences after stimulation by antigen and helper T cells. After repeated stimulation by antigen, B cells will favor more effective antibodies—a process called *affinity maturation*. This process greatly increases antibody effectiveness.

- 20) The function of spliceosomes during antibody production is to:
- A. cleave introns from the RNA and ligate the fragments.
  - B. condense the exons into smaller units.
  - C. induce conformational changes in the DNA to allow splicing.
  - D. prevent the transcription of the unused V and J regions.
- 21) According to combinatorial diversification, how many different light-chain V regions can the DNA in figure 1 produce?
- A.  $5 \times 40$
  - B.  $40 \times 5 \times 15$
  - C.  $50 \times 4$
  - D.  $40 \times 40 \times 15$
- 22) Linked genes are:
- A. Located on different chromosomes of the same size and shape.
  - B. located on the same chromosome.
  - C. rarely segregated to the same gamete during meiosis
  - D. silenced through translational repression more often than unlinked genes.
- 23) What is the most likely mechanism through which affinity maturation is able to improve the host's defenses?
- A. B cells expressing lower-affinity receptors are stimulated by the antigen to survive and proliferate, whereas other B cells survive and proliferate.
  - B. B cells expressing higher-affinity receptors are stimulated by the antigen to survive and proliferate, whereas other B cells undergo apoptosis.
  - C. B cells expressing lower-affinity receptors are stimulated by the antigen to undergo apoptosis, whereas other B cells undergo apoptosis.
  - D. B cells expressing higher-affinity receptors are stimulated by the antigen to undergo apoptosis, whereas other B cells survive and proliferate.
- 24) Which of the following mechanism(s) for promoting genetic diversity does the human body possess?
- I. Crossing over
  - II. Sexual reproduction
  - III. Spontaneous mutations
- A. I only
  - B. I and II only
  - C. II and III only
  - D. I, II and III

## Answers and Explanations

### Content Quiz

1) Enzyme B is introduced to a reaction for which the reactants are substrates to enzyme B. Which of the following will occur?

- A. The forward and reverse reactions will proceed slower.
- B.  $K_{eq}$  for the reaction will increase.
- C. The rate at which the equilibrium is reached is decreased.
- D. The rate at which the equilibrium is reached is increased.**

**Explanation: D is correct. Enzymes act to lower the activation of the reaction, which allows both the forward and reverse reaction rate to occur faster. They do not affect equilibrium.**

2) Which of the following will NOT be oxidized in the presence of  $KMnO_4$ ?

- A. t-butyl alcohol**
- B. Heptanol
- C. 2-propanol alcohol
- D. *cis*-2-pentene

**Explanation: A is correct. Tertiary alcohols are not oxidized in the presence of oxidizing agents like  $KMnO_4$ . Forming a new C-O bond would require the cleavage of a C-C bond.**

3) The carbonyl carbon is very:

- A. electrophilic.**
- B. nucleophilic.
- C. acidic.
- D. basic.

**Explanation: A is correct. The carbon is double bonded to a very electronegative oxygen atom. This draws much of the electron density off of the carbon atom, making the carbon electron poor. This results in a very electrophilic (e loving) atom.**

4) Rank the following molecules in order of increasing acidity.

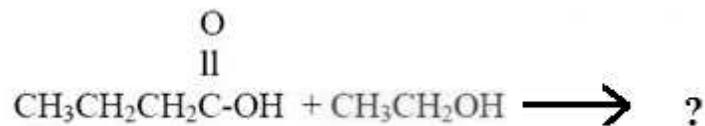
- I.  $CH_3CH_2CH_2ClCOOH$
- II.  $CH_2ClCH_2CH_2COOH$
- III.  $CH_3CH_2CH_2FCOOH$

- A.  $III < II < I$
- B.  $II < III < I$
- C.  $I < II < III$
- D.  $II < I < III$**

**Explanation: D is correct. Identify the extreme first. This tests inductive effects on molecular stability. The more electronegative the substituent on the molecule, the more acidic the molecule.**

The closer the EN group is to the acid group, the more acidic the molecule. The more EN groups there are on the atom, the more acidic the molecule is. III has the most EN substituent closest to the acid group, making it the most acidic. II has a weaker EN group further from the acid group compared to I. Thus the ranking is III > I > II.

5) What is the most likely product of the following reaction?



- A. Ethyl butanamide
- B. Hexanoic acid
- C. **Ethyl butanoate**
- D. 1-ethyl propanoic acid

**Explanation:** C is correct. The nucleophilic attack of an alcohol on a carboxylic acid will yield an ester. Even if you don't know your IUPAC rules yet, all esters end in the suffix -oate.

## Effective Reading in the Sciences

Owing to its large size, the **Golgi apparatus** (GC) was one of the first organelles to be discovered and observed in detail. Cells synthesize a large number of different macromolecules. The Golgi apparatus is integral in modifying, sorting, and packaging these macromolecules for cell secretion or use within the cell. It is essential to the compartmentalized eukaryotic cell. **Pharmaceuticals** that **interrupt** the efficiency of the Golgi apparatus **reduce** cell **viability** and can serve as valuable **cancer treatments**.

**Key terms:** golgi apparatus, pharmaceutical interruption, cancer treatment

**Cause-and-Effect:** Golgi function is important for cell viability, interruption can kill cell, possibly be used as medical treatment.

ADP-ribosylation factor 3 (**Arf3**) is responsible for the recruitment of cytosolic coat protein complexes (COPs) and subsequent retrograde transport from the Golgi apparatus. Arf3 is **activated** by **guanine nucleotide** exchange factors, which substitutes guanosine triphosphate (GTP) for guanosine diphosphate (GDP). Upon GTP substitution, Arf3 is rearranged and releases the N-terminus of the polypeptide chain from a site in the protein and instigates their sequestration to phospholipid bilayers. Through its coupling with a bilayer, Arf3 further facilitates vesicle formation by the recruitment of the coatomer protein complex COP-1 (subunits are represented by  $\beta\gamma\delta\zeta$ ). The Arf3 **GTPase** activating protein catalyzes the conversion of Arf3-bound GTP to GDP, **inactivating** the **protein**. GTPase activity is increased by Arf3 binding to **COP-1**.

**Key terms:** Arf3, activation, COP-1, Arf3 GTPase, inactivates protein

**Contrast:** Arf3-GTP is active, while Arf3-GDP form is inactive.

**Cause-and-Effect:** The entire Arf3 activation/inactivation pathway is outlined, but focus on the big picture. GTP substitution activates Arf3, which releases a polypeptide and connects with phospholipid layers of the cell. Upon phospholipid binding, Arf3 complexes with COP-1. Finally GTPase cleaves the GTP back to GDP, inactivating the Arf3 protein.

**Angiogenesis**, the formation of new blood vessels, is an essential step for cancer progression. This formation is inhibited in part by the mechanism of **monensin A**, an **inhibitor** of protein **transport** from the endoplasmic reticulum to the Golgi apparatus. Monensin A has been shown to reduce Arf3-driven cell surface vascular endothelial growth factor receptor (VEGFR) expression on endothelial cells in culture, resulting in **reversible** interruption of the Golgi apparatus and partial remission *in vitro*. Due in part to low tissue uptake, monensin A is not an effective anti-cancer agent; but, it has led to the recognition of deoxymannojirimycin (**DMNJ**) as a promising cancer **therapeutic**.

**Key terms:** Angiogenesis, Monensin A, transport inhibitor, reversible interruption, DMNJ

**Cause-and-Effect:** Monensin A reduces VEGFR expression on endothelial cells, which can block (reversibly) the actions of the golgi complex. Monensin A is no good for cancer treatment, but DMNJ may be.

6) The gene products that are packaged in Arf3 -COP vesicles are most likely destined for:

A) the smooth endoplasmic reticulum.

**B) the rough endoplasmic reticulum.**

- C) the lysosomes.  
D) the nucleolus.

Explanation: B is correct. The passage states that Arf3-COP undergoes retrograde transport. Protein translation principally occurs on the ribosomes at the rough endoplasmic reticulum (RER). The proteins are then transported to the Golgi apparatus for post translational modification, processing, and packaging for proper localization. Retrograde transport would reverse the motion and return the protein to the RER.

A: Protein translation principally occurs on the ribosomes at the rough endoplasmic reticulum (RER).

B: Is correct.

C: Protein translation principally occurs on the ribosomes at the rough endoplasmic reticulum (RER).

D: Protein translation principally occurs on the ribosomes at the rough endoplasmic reticulum (RER).

7) Which of the following is the likely outcome of hydrolysis of a  $\zeta$  phosphate group from an Arf3-bound GTP?

- A) Loss of primary protein structure  
B) Protein-membrane binding  
C) Protein activation  
**D) Protein inactivation**

Explanation: D is correct. Hydrolysis of GTP would result in the formation of GDP in the pocket, which, based on the information in the passage, is the inactive form.

A: According to paragraph 2, loss of  $\text{PO}_4$  from Arf3 results in protein inactivation.

B: According to paragraph 2, loss of  $\text{PO}_4$  from Arf3 results in protein inactivation.

C: According to paragraph 2, loss of  $\text{PO}_4$  from Arf3 results in protein inactivation.

D: Is correct.

8) Which of the following enzymes performs a similar function to the Arf3 GTPase activating protein?

- A) Pyruvate Kinase  
B) Lactate dehydrogenase  
**C) Alkaline phosphatase**  
D) Peptidyl transferase

Explanation: C is correct. According to the passage, the GTPase "...catalyzes the conversion of Arf3-bound GTP to GDP, inactivating the protein." Phosphatases are a class of hydrolase responsible for the cleavage of phosphate bonds utilizing water to remove an inorganic phosphate.

A: Pyruvate kinase is an enzyme involved in glycolysis. It catalyzes the transfer of a phosphate group from phosphoenolpyruvate to ADP, yielding one molecule of pyruvate and one molecule of ATP.

B: A dehydrogenase is an enzyme that transfers a hydride from one molecule to another. Lactate dehydrogenase catalyzes the conversion of pyruvate to lactate and back, as it converts NADH to  $\text{NAD}^+$  and back.

C: Is correct.

D: Peptidyl transferase is an aminoacyltransferase as well as the primary enzymatic function of the ribosome, which forms peptide bonds between adjacent amino acids using tRNAs during the translation process of protein biosynthesis.

9) The mechanism of Monensin A described in the passage indicates that the drug would be best used to treat:

- A) bacterial infection by *Bacillus anthracis*.
- B) viral infection by *Varicella zoster*.
- C) bacterial infection by *Salmonella enterica*.
- D) fungal infection by *Candida albicans*.**

Explanation: D is correct. The passage states that Monensin A disrupts the Golgi apparatus, and of the choices, only *Candida* (a eukaryotic fungus) have a Golgi apparatus.

- A: Prokaryotes like *Bacillus a.* have no Golgi apparatus.
- B: Virus like *Varicella z.* have no Golgi apparatus.
- C: Prokaryotes like *Salmonella e.* have no Golgi apparatus.
- D: Is correct.

10) GTP is classified as a member of which class of biological molecules?

- A) Amino acids
- B) Peptides
- C) Nucleotides
- D) Nucleic Acids**

Explanation: D is correct. GTP stands for guanosine tri-phosphate, which is a nucleotide. Nucleotides are organic molecules that serve as the monomers, or subunits, of nucleic acids like DNA and RNA. Nucleotides are composed of a nitrogenous base, a five-carbon sugar (ribose or deoxyribose), and at least one phosphate group.

- A: Amino acids are composed of amine (-NH<sub>2</sub>) and carboxylic acid (-COOH) functional groups, along with a side-chain specific to each amino acid
- B: Peptides short chains of amino acid monomers linked by peptide (amide) bonds.
- C: Is correct.
- D: Nucleic acids are polymeric macromolecules, which include DNA (deoxyribonucleic acid) and RNA (ribonucleic acid), are made from multiple monomers (known as nucleotides) bonded together.

11) One of the problems in certain forms of Schizophrenia is a loss-of-function mutation to peptidyl transferase. What process is most likely to be halted in these patients?

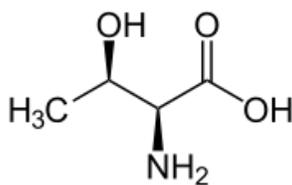
- A. Binding of the mRNA template to the

ribosome

- B. Construction of the cellular ribosome
- C. Construction of the primary structure of neuroproteins**
- D. tRNA recognition of mRNA codons.

**C is correct. Peptidyl transferase is important for the formation of peptide bonds.**

12) A polar-substrate binding enzyme is most likely to have threonine residues richly populating which region? :



- A. The interior of the enzyme.
- B. The exterior of the enzyme.
- C. The active site of the enzyme.**
- D. Within an alpha-helical structure.

**C is correct. Threonine has an additional property that is frequently overlooked. Like Valine, and Isoleucine it is C-beta branched. Whereas most amino acids contain only one non-hydrogen substituent attached to their C-beta carbon, these three amino acids contain two. This means that there is a lot more bulkiness near to the protein backbone, and thus means that these amino acids are more restricted in the conformations the main-chain can adopt. Perhaps the most pronounced effect of this is that it is more difficult for these amino acids to adopt an alpha-helical conformation, though it is easy and even preferred for them to lie within beta-sheets. Threonines are quite common in active sites. The hydroxyl group is very reactive, being able to form hydrogen bonds with a variety of polar substrates.**

## Practice Passage 2

Voltage-gated **sodium (Nav) channels** are responsible for propagating action potentials. **Humans** contain a complex repertoire of **nine** Nav channel **subtypes** denoted Nav1.1–Nav1.9. **Nav1.7** plays a crucial role in the human **pain signaling** pathway and it is an important therapeutic target for treatment of chronic pain.

**Key terms: sodium (Nav) channels, nine subtypes, Human Nav1.7 pain signaling**

**Cause-and-Effect: Human Nav1.7 protein activity helps regulate pain detection.**

A scientist sought to **determine** the diversity of **Nav1.7-active peptides** in the **venom** of an Australian tarantula and to characterize their **potency** and subtype **selectivity**. **Three** tarantula **peptides** were **reduced** and **alkylated** using the volatile reagent triethyl-phosphine, prior to tryptic digestion. The **mass** of each peptide was found to increase by 270 Da following reduction/alkylation.

**Key terms: determine venom in Nav1.7 potency, selectivity, three peptides, reduced/alkylated mass increase.**

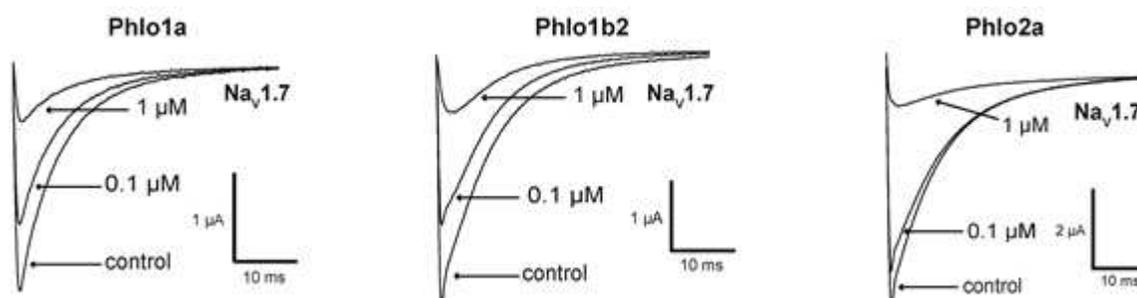
**Cause-and-Effect: 270 Da mass increase after reduction/alkylation, coupled with disulfide data mentioned in paragraph 5, indicates the presence of six cysteine residues (i.e., the addition of six ethanolyl groups of 45 Da each) that form three disulfide bonds.**

Next the three **peptides** were **isolated**. TRTX-**Phlo1a**, **-Phlo1b** and **-Phlo2a**, inhibit **human Nav1.7** (hNav1.7). Phlo1a and Phlo1b are 35-residue peptides that **differ** by their **C-terminal** amino acid. The partial sequence of **Phlo2a** revealed extensive **positively charged residues** *in vitro*. Human oocytes were treated with each peptide and  $IC_{50}$  (how much of a particular substance is needed to inhibit a given biological process by half) and  $V_{0.5}$  (the voltage at which the channels are half-maximally activated) was measured for each of the peptides. Phlo1a and Phlo1b inhibit hNav1.7 with  **$IC_{50}$  values** (mean  $\pm$  S.E.M) of  $439 \pm 46$  and  $400 \pm 61$  nM, respectively, with only minor activity on hNav1.5. Although similarly potent at hNav1.7 ( $IC_{50}$   $333 \pm 19$  nM), Phlo2a also potently inhibited hNav1.2 and hNav1.5.

**Key terms: Phlo1a, Phlo1b, Phlo2a, inhibit human Nav1.7, differ in C-terminal, Phlo2a positively charged residues,  $V_{0.5}$ ,  $IC_{50}$  values**

**Contrast: Phlo1a/b structures are very similar while 2a has extensive + charges. 1a/b are Nav1.7 specific while 2a had wider inhibition activity.**

**Cause-and-Effect: Positively charged residues on 2a may play a role in its expanded activity while the 1 amino acid difference b/w 1a/b causes no significant diff in effect as measured by  $IC_{50}$ .**

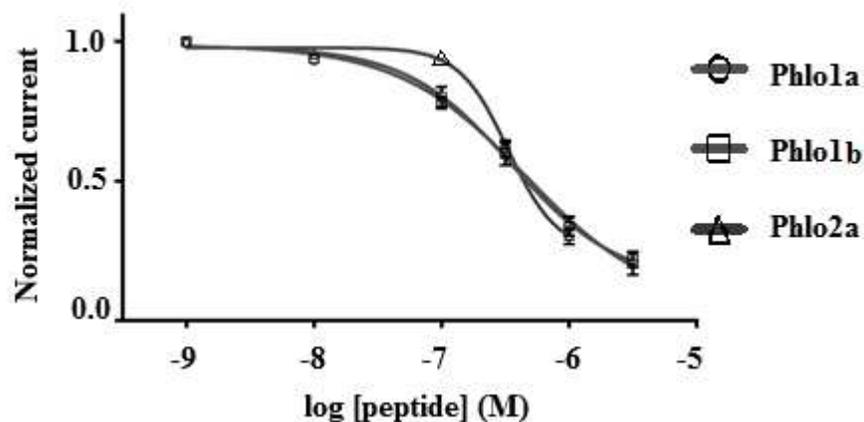


**Figure 1** Effects of venom peptides on hNav1.7 expressed in oocytes

Whole-cell Na current traces were made on all three peptides in the **absence and presence** of 0.1 or 1  $\mu\text{M}$  peptide (figure 1). Sodium currents were evoked by a 50-ms step depolarization to 0 mV from a holding potential of  $-80$  mV every 10 s. **Mean  $V_{0.5}$**  for the Nav1.7 channel was observed to **shift** from  $-18$  mV to  $-12$  mV and  $-8$  mV. **Concentration-effect curves** for **inhibition** of hNav1.7 by Phlo1a, Phlo1b and Phlo2a ( $n = 15$ ) were recorded as well (figure 2).

**Key terms:** Na current traces, absence and presence of peptide, Mean  $V_{0.5}$  shift, concentration-effect curve, inhibition

**Cause-and-Effect:** Each cell was given a depolarizing stimulus from rest. As [peptide] increased, the effect was more pronounced. Membrane potentials rose (depolarized) in response to peptide treatment.



**Figure 2** All 3 peptides have  $IC_{50}$  values between  $10^{-7}$  and  $10^{-6}$  M with Phlo2a having a steeper curve/more potent effect in this concentration range.

The majority of tarantula-venom peptides are 3.0–4.5 kDa in size and highly disulfide-bridged. These bridges allow them to form a highly stable knot fold that provides resistance to chemical and thermal degradation as well as proteases. Numerous spider venom peptides have been shown to modulate the activity of Nav channels and these peptides represent a rich source of research tools and therapeutic lead molecules.

**Key terms:** peptides size, disulfide-bridged, provides resistance

**Cause-and-Effect:** The extensive disulfide links allow the venom to form stable knot-like structures that protect it from environmental degradation.

- 13) What is the effect of the spider-venom peptides on channel activity?
- All three peptides inactivate the S4 helix in hNav1.7 channels.
  - All three peptides cause a depolarizing shift in the voltage-dependence of hNav1.7 activation.**
  - All three peptides cause a hyperpolarizing shift in the voltage-dependence of hNav1.7 activation.
  - All three peptides cause the cell membrane to transition from resting to polarized.

**Explanation:** B is correct. From the data shown in figure 1, we can see all three peptides inhibited Na current activity in a dose-dependent manner. In addition,  $V_{0.5}$  for activation of hNav1.7 was

moved to more *positive* (-18 mV to -8 mV) potentials in a concentration-dependent manner. This would suggest that the Phlo peptides are depolarizing (making the membrane potential more +) gating modifiers that inhibit channel activation via interaction with one or more voltage-sensor domains.

A: This is not true. Voltage-gated sodium channels and calcium channels are made up of a single polypeptide with four homologous domains. Each domain contains 6 membrane spanning alpha helices. The S4 helix is the voltage sensing helix. It has many positive charges such that a high positive charge outside the cell repels the helix, keeping the channel in its closed state. Depolarization of the cell interior causes a conformational change such that ions may flow through the channel. If the peptides inactivated the voltage-sensor domains of the channels, they would have been unable to respond to the stimuli provided in the experiment.

B: Is correct.

C: The current shift in figure 1 along with the  $V_{0.5}$  increase indicates that the resting potential becomes more +, indicating a *depolarizing* effect.

D: Polarization refers to a separation of charges across a membrane. This is in effect across the cell membrane at all times, and is not the direct result of the peptides (for example, the degree of polarization at the resting potential).

14) A central aspect of developing new anesthetics is the specificity of the agent's signaling. Based on the data from the experiment, which of the peptides would be LEAST effective as an anesthetic?

- A. Phlo1a
- B. Phlo2b
- C. Phlo2a**
- D. Phlo1b

**Explanation: C is correct. The experiment showed that Phlo2a also potently inhibited hNav1.2 and hNav1.5, meaning the peptide was NOT as specific to the Nav1.7 channels as the other 2 peptides.**

A, D: According to paragraph 3, both of these peptides only exhibited activity with the  $Nav_{1.7}$  channels.

B: There was no protein Phlo2b tested by the researchers.

C: Is correct.

15) Which of the following would best explain the reason for the variance observed in channel effect by the peptides studied?

- A. Phlo1a has a significantly lower molecular weight than the Phlo2a and Phlo1b peptides.
- B. Phlo2a has a lower  $IC_{50}$  compared to Phlo1a and Phlo1b.
- C. C-terminal residues influence  $Nav$  subtype selectivity of venom peptides.
- D. Phlo2a binds to the channel at multiple sites with positive cooperativity.**

**Explanation: D is correct. Looking at figure 2, we notice that the slope of the concentration-effect curve for Phlo2a inhibition of hNav1.7 currents was steeper compared with that of Phlo1a and Phlo1b, meaning that it binds to its receptors more strongly as [peptide] increases than the other 2 peptides. This may result if the peptide could bind to the channel at multiple sites with positive cooperativity.**

A: We do not know anything about the relative weights of each peptide. It may be true that the Phlo1a is much smaller than the other 2 peptides and it could explain a difference between 1a and 1b activity. The problem with this choice is that figure 2 and paragraph 3 inform us that Phlo1a and Phlo1b exhibit almost exactly the same behavior on Na channels while the Phlo2a effect differs greatly. Thus, it is unlikely that a weight difference between 1a and 1b would explain this observed difference.

B: This is true, as it is the relationship we get from the passage. But, this choice does not answer the question given, which is WHY this difference exists.

C: This is a tempting answer. Phlo1a and Phlo1b do exhibit slightly different IC<sub>50</sub> values and the passage states that they differ only in their C-terminal residue. However, we are given standard error of the mean (SEM) data for these IC values. SEM quantifies how precisely you know the mean, taking into account both the std. deviation and sample size. Looking at whether the SEM (which =  $\text{std. dev} / \sqrt{n}$ ) bars overlap lets you compare the difference between the mean with the precision of those means. A good rule of thumb you can use for test day is that if two SEM ranges do overlap, and the sample sizes are equal or nearly equal, then you know that the P value is (much) greater than 0.05, so the difference is not statistically significant.

D: Is correct.

16) Which amino acid is most likely to be found protecting the receptor binding areas on the venom peptides discussed in the passage?

- A. M
- B. H
- C. C
- D. W

**Explanation: C is correct. Of all the naturally occurring amino acids, only methionine and cysteine contain sulfur. This question asks about which of the AA would be most likely. To protect the receptor binding site, the residues would need to be on the exterior (hydrophilic environment) of the protein. While both M and C are non-polar and largely hydrophobic, cysteine can ionize to yield the polar, hydrophilic thiolate anion.**

A: Methionine is one of the most hydrophobic amino acids and is almost always found on the interior of proteins.

B: Histidine does not contain sulfur which is necessary for disulfide links.

C: Is correct.

D: Tryptophan does not contain sulfur which is necessary for disulfide links.

17) Nodes of Ranvier act as relays for myelinated neuron signaling. How might the action potentials of such a neuron be affected if the intermodal distances were increased significantly?

- A. Action potentials might fail to traverse the axon.**
- B. Action potentials might travel slower than their normal velocity.
- C. Action potentials would travel faster than their normal velocity.
- D. Action potentials would remain unaffected due to the all-or-nothing response.

**Explanation: A is correct. Myelinated axons have far fewer sodium channels in the internodal (myelin covered) region compared to the bare nodes. Rather, the potential change produced by the**

**action potential at one node spreads in the internodal region along the axon passively just as the temperature would spread along a long metal rod. The potential spreads, but gets smaller, just as a temperature change induced at one end of a rod would get smaller as it spreads along a rod. If the internodal space were sufficiently large, the AP would diminish to 0 by the time it traverses the internodal distance.**

A: Is correct.

B: If nodes are closer together, the AP might travel more slowly, but here the internodal space is increased.

C: If the internodal space were only increased a small amount, then some research has shown that AP velocities can increase but it is far from guaranteed. Even if you were not aware of this knowledge, the question states that the internodal distance is being increased by a very large factor, indicating the change could be drastic.

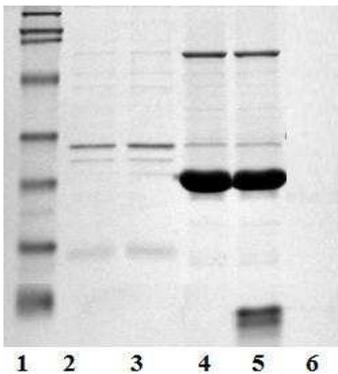
D: The “all-or-nothing” response refers to the fact that the magnitude of action potentials fired by axons is independent of the strength of the stimulus, much the same way a height requirement works on an amusement park ride. Whether you are 1 inch or 1 foot taller than the minimum height, so long as you are over the minimum height, you experience the same ride as everyone else allowed on. If internodal space were changed, AP velocity could be affected.

18) Part of the PCR process involves heating up the DNA prior to the addition of RNA primers. A point is reached at which the DNA molecules exist as single strands. Which of the following DNA sequences will require the highest temperature to achieve this?

- A. 5'-ATTCTGCTATTA-3'
- B. 5'-ATGCUUUTATTA-3'
- C. 5'-GTTCTGCTATTA-3'
- D. 5'-ACGCCTGCTAGC-3'**

**D is correct. G and C form the hydrogen with each other while A and T/U form 2 hydrogen bonds. Thus, the more GC rich the strand, the stronger it is and the greater a denaturing temperature is required.**

19) Agarose gel electrophoresis is performed on DNA obtained after an experiment run on portions of gene A. If lanes 4 and 5 used the same protocol, which of the following best explains the additional band in lane 5?



Lane 1 is a ladder of DNA fragments from 50 to 400 bp in length.

- A. The sample in lane 5 was contaminated with DNAses.
- B. DNA primers used hybridized to each other and were amplified, generating larger fragments along with the desired fragment.
- C. The sample in lane 5 was contaminated with genomic DNA.**
- D. Preparation of the sample for lane 4 mistakenly forgot to remove an intron.

**C is correct. The figure shows fragments of increasing size as we travel down the gel (50 – 400 BP). Lane 5 shows a large fragment of DNA that was unable to travel through the gel. This fragment is much larger than anything in lane 4 and larger than all of the material shown in lane 4 combined. Thus it is unlikely to be a fragment or combination of fragments of gene A.**

## Practice Passage 3

The variety of human **antibodies**, over  **$10^{12}$  different molecules**, poses a unique genetic problem: how can a human, whose genome contains fewer than 50,000 genes, make more antibodies than there are genes in its genome? The mammalian immune system has evolved unique **genetic mechanisms** that enable it to **generate** an **enormous number** of different antibodies by joining separate gene segments together before they are transcribed.

**Key terms:** antibodies,  $10^{12}$  different molecules, genetic mechanisms, generate enormous number

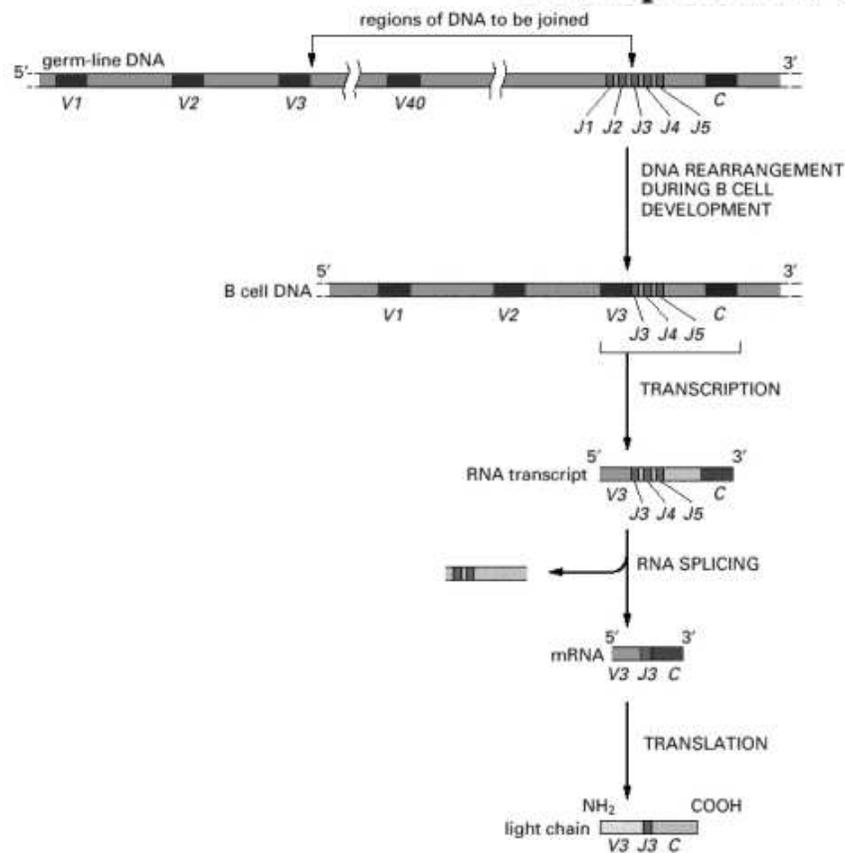
**Cause and Effect:** Through the joining of separate gene segments, the human body can generate billions of times more antibodies than it has genes.

**Antibodies** are **produced** from **three pools** of gene segments and exons. In each pool, separate gene segments that code for different parts of the variable region of the light or heavy chains are brought together by site-specific recombination during B cell development. The combinatorial joining of these segments, called ***combinatorial diversification***, greatly increases this variety. **Light-chain** pools contain one or more constant- (C-) region exons and sets of variable (V) and joining (J) gene segments. The **heavy-chain** pool contains sets of C-region exons and sets of V, diversity (D), and J gene segments. A  $V_L$  gene segment recombines with a  $J_L$  gene segment to produce a DNA sequence coding for the V region of a light chain, and a  $V_H$  gene segment recombines with a D and a  $J_H$  gene segment to produce a DNA sequence coding for the V region of a heavy chain. Each of the assembled V-region coding sequences is then **co-transcribed** with the appropriate C-region sequence to **produce an RNA** molecule that codes for the complete polypeptide chain. The light chain portion of this synthesis is shown in figure 1.

**Key terms:** Antibodies produced, three gene pools, *combinatorial diversification*, C V J D, Light-chain, heavy-chain, co-transcribed

**Contrast:** Light chains have 2 variable regions while heavy chains have 3.

**Cause and Effect:** The heavy and light chains are combined to create even more potential antigen binding regions. Heavy = VJDC, Light = VJC



**Figure 1 Both used and unused regions are transcribed before unused regions are removed before translation**

In the “**germ-line**” DNA the cluster of **five J gene** segments is separated from the C-region exon by a short intron and from the **40 V gene** segments by thousands of nucleotide pairs. During the **development** of a **B cell**, the **randomly chosen** V gene segment is moved to lie precisely next to one of the J gene segments. The extra J gene segments and the intron sequence are transcribed (along with the joined V3 and J3 gene segments and the C-region exon) and then removed by **RNA splicing** to generate mRNA in which the chosen V, J, and C sequences are contiguous. These mRNAs are then translated into light chains. A J gene segment encodes the C-terminal 15 amino acids of the **V region**, and the **V-J segment** junction coincides with the **third hypervariable region** of the light chain, which is the **most variable** part of the V region.

**Key terms:** germ-line DNA, 40 V genes, five J genes, development of B cell, randomly chosen, RNA splicing, V region, V-J segment third hypervariable region/ most variable

**Contrast:** The extra J segments are transcribed but the extra V segments are not.

**Cause and Effect:** This is a description of the mechanism shown in figure 1. There are 40 V segments that can randomly combine with 5 J segments to form  $40 \times 5 = 200$  different combinations, not counting the mutations that can occur in the active site.

Because the **antigen-binding site** is formed where the hypervariable **loops** of the **V<sub>L</sub>** and **V<sub>H</sub>** come together, the heavy and light chains can pair to form **millions** of **different** antigen-binding sites. This number is greatly increased by **the loss and gain of nucleotides** at the site of gene-segment joining, as well as by **somatic mutations** that occur with very high frequency in the assembled V-region coding sequences after stimulation by antigen and helper T cells. After repeated stimulation by antigen, B cells will favor more effective antibodies—a process called **affinity maturation**. This process greatly increases antibody effectiveness.

**Key terms:** antigen binding site,  $V_L$  and  $V_H$  loops, millions of different Ab, the loss and gain of nucleotides, somatic mutations, *affinity maturation*

**Cause and Effect:** Since the antigen binding site is a combination of both chains, we can get  $V_L \times V_J \times J_L \times J_H \times D$  different combinations, plus sporadic mutations and nucleotide changes. B cells can favor better antibodies though maturation process which favors “effective” antibodies.

20) The function of spliceosomes during antibody production is to:

- A. cleave introns from the RNA and ligate the fragments.**
- B. condense the exons into smaller units.
- C. induce conformational changes in the DNA to allow splicing.
- D. prevent the transcription of the unused V and J regions.

**Explanation: A is correct. The spliceosome removes introns from a transcribed pre-mRNA, a kind of primary transcript.**

A: Is correct.

B: DNA is condensed by histone proteins, not spliceosomes.

C: Conformational changes are handled by enzymes like helicase and topoisomerases, not by spliceosomes.

D: According to the passage, ALL of the regions are transcribed, including the introns and unused V and J regions.

21) According to combinatorial diversification, how many different light-chain V regions can the DNA in figure 1 produce?

- A. 5 x 40**
- B. 40 x 5 x 15
- C. 50 x 4
- D. 40 x 40 x 15

**Explanation: A is correct. According to the passage, each light chain is built by combining 1 element each from the available V and J regions. The 3<sup>rd</sup> paragraph states that there are 5 J regions and 40 V regions. This results in 40 x 5 different combinations.**

A: Is correct.

B, C, D: There are only 2 variable elements to a light chain, V and J. There are 5 J regions and 40 V regions. Do not be tempted by C which incorrectly does the combination, though the mathematical result is the same.

22) Linked genes are:

- A. Located on different chromosomes of the same size and shape.
- B. located on the same chromosome.**
- C. rarely segregated to the same gamete during meiosis
- D. silenced through translational repression more often than unlinked genes.

**Explanation: B is correct. Genetic linkage is the tendency of alleles that are located nearby each other on the same chromosome to be inherited together during meiosis. The likelihood of their linkage is inversely proportional to how far apart they are on the chromosome. In other words, the nearer two genes are on a chromosome, the lower is the chance of a swap occurring between them, and the more likely they are to be inherited together or “linked.”**

A: Linked genes are located on the same chromosome.

B: Is correct.

C: Since linked genes are on the same chromosome and since chromosomes are passed on to offspring as units, linked genes are normally inherited together.

D: Linked genes are silenced no more or less often than any other gene.

23) What is the most likely mechanism through which affinity maturation is able to improve the host's defenses?

A. B cells expressing lower-affinity receptors are stimulated by the antigen to survive and proliferate, whereas other B cells survive and proliferate.

**B. B cells expressing higher-affinity receptors are stimulated by the antigen to survive and proliferate, whereas other B cells undergo apoptosis.**

C. B cells expressing lower-affinity receptors are stimulated by the antigen to undergo apoptosis, whereas other B cells undergo apoptosis.

D. B cells expressing higher-affinity receptors are stimulated by the antigen to undergo apoptosis, whereas other B cells survive and proliferate.

**Explanation: B is correct. In order for the body's immune system to grow stronger, proper antibodies must be allowed to grow and expand. This means that B cells with a high affinity for the target antigen would need to be preferentially nurtured while those B cells with low affinities should be killed off.**

A, C, D: Antibodies with a high affinity should be favored, while those with low affinities should be eliminated.

B: Is correct.

24) Which of the following mechanism(s) for promoting genetic diversity does the human body possess?

**I. Crossing over**

**II. Sexual reproduction**

**III. Spontaneous mutations**

A. I only

B. I and II only

C. II and III only

**D. I, II and III**

**Explanation: D is correct. All of these mechanisms are primary sources of genetic variation in the human species.**

I. Chromosomal crossover (or crossing over) is the exchange of genetic material between homologous chromosomes that results in recombinant chromosomes. It is one of the final phases of genetic recombination, which occurs during prophase I of meiosis.

II. Sex can introduce new gene combinations into a population. This genetic shuffling is another important source of genetic variation.

III. Genetic mutations, random changes to the genetic code, contribute to the genetic variability within a population and can have positive, negative, or neutral effects on fitness

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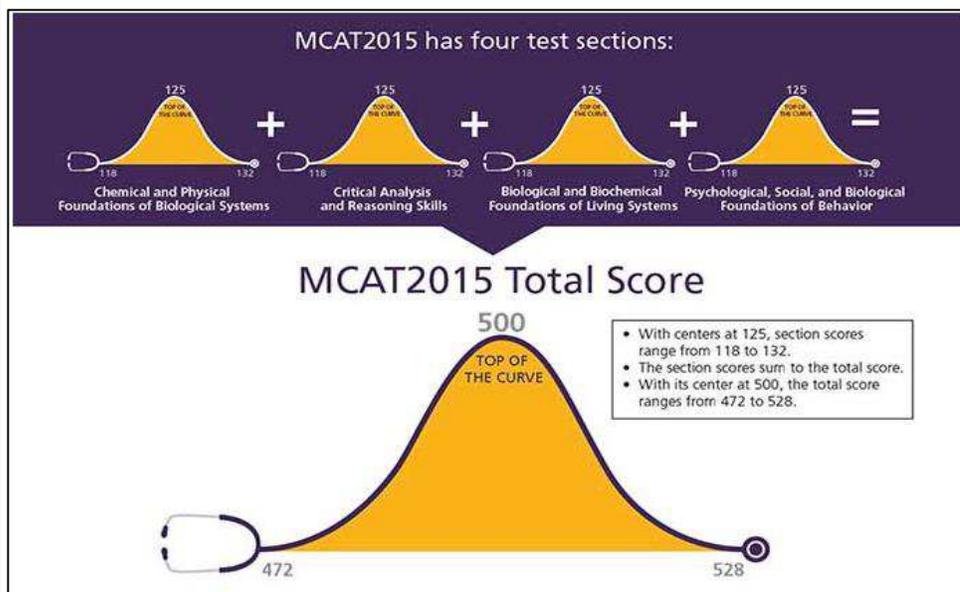
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- **[Next Step's Free Half Length Diagnostic Exam:](#)** If you are preparing for the MCAT then you need to take this test. It will take about 4 hours and includes full answers and explanations for every question. This resource will help you identify your strengths and areas of opportunity when you start your prep.
- **[AAMC 2015 MCAT Practice Test Review Video Series:](#)** Every student should take the official AAMC Practice Test. This free video series reviews each section to help students understand their results on the test after they have taken it.
- The Critical Analysis and Reasoning Section is often the most challenging for pre-med students. This free video course provides an overview of strategies that will help you tackle this section of the test: **[Click here to access this free video course!](#)**
- **[Click here](#)** to sign up for our MCAT question of the day emails for great, free, practice content throughout the week.
- **[Click here](#)** for our MCAT blog.

## Additional MCAT resources for sale from Next Step

- **[Next Step's MCAT Book Store:](#)** Next Step has published a nine book series to help students prepare for the new MCAT. These books are a great addition to any students MCAT library and we are unrivaled when it comes to prep for the verbal section of the new MCAT.
- **[Next Step's Full Length Practice Tests:](#)** Next Step has created 5 full length practice tests for the new MCAT.



### MCAT Pre-Reqs Next Step Suggests:

Biology: 2 to 3 semesters  
 Chemistry: 2 semesters  
 O-Chem: 1 to 2 semesters  
 Physics: 2 semesters  
 Biochemistry: 1 semester  
 Psychology: 1 semester  
 Sociology: 1 semester  
 Statistics: 1 semester  
 Humanities: 1-3 semesters