Using the Immune System as a Model for Studying Cell Communication: Toll-like Receptor 2 (TLR2) Polymorphisms, Signaling Function, and Human Disease

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Funded by the American Association of Immunologists –
John H. Wallace High School Teacher Summer Research Program

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Toll-like Receptor 2 (TLR2) Polymorphisms, Signaling Function and Human Disease

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With the goal of introducing high school students to the molecular mechanisms governing health and disease, I recently developed a course entitled, "The Cell and Molecular Basis of Human Health and Disease", which offers an exploration of how such fundamental processes as gene regulation, cell communication, and cell death form the basis of health and disease. To enhance the immunology unit within this course, I have developed a curriculum based on my summer research through the AAI that is focused on current understanding of host antimicrobial innate defense and the impact of polymorphisms within Toll-like receptor (TLR) 2. Using transfection-based complementation of HEK293 cells, we found that R753Q inhibits TLR2-mediated activation of NF-kB and expression of IL-8 but does not affect TLR2 expression. Students will learn the basics of TLR innate defense, study TLR expression/functions and how expression of inflammatory cytokines is controlled by transcription factors, and how polymorphisms in TLR2 are associated with infectious diseases. Students will engage in internet-based research about infectious and inflammatory diseases and how the etiology of these diseases is controlled by changed functionality of polymorphic TLR2. Upon completion of this curriculum, students will have developed a deeper understanding of the molecular mechanisms governing innate immunity, as well as the theoretical concepts of common lab assays used to study TLR expression and functions.

II. Teacher's Guide

A. Introduction – Why use this curriculum?

A growing need for Biomedicine in the High School Biology curriculum

Technological advances made in the past few decades in the field of cell biology have revolutionized our understanding of the molecular mechanisms that govern life. In turn, the sharing of pertinent biomedical discoveries with the general public has become increasingly common in the media. These advances in our understanding have posed a challenge to the High School Biology curriculum, as teachers seek out new curricular strategies that will ensure that their students will not *only* be exposed to biological concepts that are consistent with current understanding, but that students will also develop a conceptual appreciation for some of the cutting-edge, experimental methodologies that scientists use in biomedical research.

The role of Cell and Molecular Biology in addressing this need

In the preface to his book entitled, *Human Molecular Biology*, Richard J. Epstein asserts: "Good health is a matter of having the right molecules in the right place at the right time (Epstein, 2003)." If biomedical research is to begin to play a pivotal role in innovating the High School Biology curriculum, it will be important that students develop an appreciation for the molecular world in which new medical paradigms are explored, tested, and refined. While this may seem to pose a conflict in that the cellular and molecular biology components of the average high school Biology course are already perceived as particularly abstract and often difficult to digest for many students, there are a number of strategies that teachers can employ that will both capture students' imagination about this molecular world and empower them to think more critically about it.

With the hope of introducing high school students to the molecular mechanisms that govern health and disease, I recently developed a biology elective entitled "The Cell and Molecular Basis of Human Health and Disease". This course offers an exploration of how such fundamental molecular processes such as cell division, cell communication, and cell death form the basis of health and disease, placing an emphasis on current 'hot topics' in biomedical research. The course begins with the fundamental assumption that, although the human body consists of trillions of cells comprising over 200 distinct types, there are several basic processes that all cells *must* carry out, and that these processes ultimately form the basis for physiological health. After reviewing the basic organelle structure of the 'typical' cell, students explore cell function through a series of seven to eight, themed units, organized by basic cellular processes such as *cells reproduce*, *cells reuse and recycle*, *cells communicate, cells age,* and *cells die.* Throughout each unit, students are given specific physiological examples in which a given cellular process plays a pivotal role.

The present curriculum comprises the *cellular communication* component of the course, and uses the innate immune system as a means of exemplifying the critical role that this cellular process plays in health and disease. My research project under the guidance of Dr. Andrei Medvedev at the University of Maryland School of Medicine enabled me to infuse current biomedical research methodologies into this unit, by exposing students to a rather specific example of how immunologists currently seek to understand the role that cell communication plays in mediating macrophage recognition and response to bacterial infections in the body.

B. Curriculum Overview

Who can use this curriculum?

As many of the topics and reading material covered are rather advanced, it is recommended that, should this curriculum be used in its entirety, it would implemented in an advanced high school biology elective, rather than in an introductory biology course. That being said, however, many of the basic concepts, individual assignments, and group projects could be used by any teacher hoping to enhance his/her instruction of cell communication and/or basic immunity.

Curriculum Outline

When implementing this curriculum, it is recommended that it be divided into two major units: *Basic Cell Biology* and *Cell Biology of the Immune System.* Each major unit should be further organized into an ***introductory*** phase, which is led primarily by the teacher, a ***student exploration*** phase, which should both challenge and empower students to use the principles they've learned to undertake interest-driven research on a related topic; and a ***practical application*** phase in which the teacher and students explore several real world examples of how the material covered can be studied in a laboratory setting. Please note that classroom-specific examples of the topics outlined below are available in the *Sample Curriculum* section of this document.

Basic Cell Biology

1. Introduction to Key Concepts

This component will contain lecture material, reading material, and class assignments that will introduce students to:

a) The basics of cell structure
b) The Central Dogma: How information flows in cells from DNA to protein and how this is important in regulating cellular activity
c) The three components cell communication (Reception, Transduction, and Response)
d) The concept of *receptor* and *ligand* and how proteins and small molecules mediate the three steps of cell communication

2. Student Exploration of Key Concepts

This component contains additional, independent projects and activities that students can do in order to further explore how cell communication plays a role in physiological health and to discern reoccurring themes in how seemingly distinct types of cell types rely on cell communication carry out such processes as:

a) Taste
b) Smell

c) Sight
d) Appetite

Cell Biology of the Immune System

1. Introduction to Key Concepts

This contains ideas and examples of lecture material, reading material, and class assignments that will introduce students to:

a) The basic functioning of the immune system
    a. The importance of immunity
    b. Innate vs Adaptive immunity
        i. Cellular components of each
        ii. Key proteins and small molecules involved
    c. Microbiology and infectious disease basics
    d. The concept of Toll-like Receptors and how, through cell communication, they enable phagocytic immune cells of the innate immune system to recognize and respond to microbial infection

2. Student Exploration of Key Concepts

This component contains additional, independent projects and activities that students can do in order to further explore:

a) specific, global infectious diseases and their impact on the immune system
b) how to use metaphorical depictions of how the immune system coordinates a response to a hypothetical infection

3. *Practical Applications*

This final component provides students practical examples of how immunology concepts they have learned can be explored in a laboratory setting, and will allow them to synthesize multiple concepts ranging from basic cell structure and the Central Dogma to cell signaling among specific immune cells during an infection. It will also provide students with a much needed technique of reading and interpreting scientific literature. Consider the following components:

a) readily accessible in-class laboratory exercises that introduce simple microscopy techniques used to:
    a. identify the cellular components of blood
    b. identify and classify bacterial pathogens
b) careful reading and group discussion of popular scientific literature relevant to innate immunity and Toll-like receptors

c) carefully guided, independent internet-based research on how scientists are currently exploring the role of Toll-like Receptor 2 in health and disease

III. Science Background and Teacher Resources

Components in the *Basic Cell Biology* unit covering cell structure and the Central Dogma should not require too much outside preparation for the average Biology teacher, as these concepts are routinely covered in any introductory Biology course; however, the following supplemental materials will be particularly useful for teacher perusal and subsequent student assigned reading/work.

Cell Structure and Function:

Inside the Cell a highly enjoyable, free publication by the National Institute of General Medical Science at the National Institutes of Health available for download at: http://publications.nigms.nih.gov/insidethecell/. Chapters relevant to the present curriculum are Chapter 1: *An Owner's Guide to the Cell* and selected sections of Chapter 2: *Cell Business Basics*. This is often the first reading assignment for students enrolled in the aforementioned *Cell and Molecular Biology of Human Health and Disease* course.

Central Dogma of Molecular Biology:

Why review this?
It is important to stress that the main purpose of covering this topic is to get students to: (1) recall a crucial component to the functioning of all cells; (2) be able to appreciate the various ways in which the activity of a specific gene can be studied. Given that, in order for a protein to be made, a segment of DNA must first be available to be transcribed into mRNA, mRNA must be spliced into a mature mRNA transcript, and the mRNA transcript must be translated into protein, it follows that the activity of a given gene could be studied at various levels, including determining whether the gene's promoter is 'on' or 'off', measuring mRNA levels, measuring protein levels, or, if the specific function of the protein is known, measuring its activity in the cell. This will become important later in the unit, when students learn about how immune cell signaling pathways are studied in a laboratory setting.

Useful resources
Some of the concepts of DNA, RNA, and proteins are covered in the above *Inside the* Cell publication, but would also be found in any introductory Biology textbook, such as Holt *Biology* or a college-level text such as *Biology – 8th Ed.* Campbell and Reece. Additional resources that are amenable to both teacher and student perusal include:

- The *Learn Genetics™* website, which provides an excellent tutorial on the basics of DNA replication, transcription, and translation.

- The following animation, which enables visualization of the flow of genetic information in a stepwise fashion: http://www.learnerstv.com/animation/biology/central_dogma.swf.

A. Cell Communication Basics

This component is not always covered in Introductory Biology curricula, and if so, not to the extent that the present curriculum requires. Thus, some background research is required by the teacher. In addition to chapters found in the aforementioned introductory or college-level Biology textbooks, the following websites are particularly helpful:

- http://kentsimmons.uwinnipeg.ca/cm1504/cellcommunication.htm - provides an excellent review of the basics of cell signaling and provide great images that could be used in handouts and/or lectures for students
- http://learn.genetics.utah.edu/content/begin/cells/insidestory/ - provides a specific example of cell communication through the fight-or-flight response, as well as an interactive tutorial on various types of ligands, their receptors, and subsequent responses.

- http://kisdwebs.katyisd.org/campuses/MRHS/teacherweb/hallk/Teacher%20Documents/AP%20Biology%20Materials/The%20Cell/Cell-to-Cell%20Communication/08_A01s.swf - a great tutorial that enables the viewer to design their own cell communication pathway!

- http://media.pearsoncmg.com/bc/bc_campbell_biology_7/media/interactivemedia/activities/load.html?11&A – great interactive animation and overview of cell signaling

Teacher background knowledge requirements for the *Cell Biology of the Immune System* unit will vary depending upon how one decides to implement this unit, but should include a review of the immune system, as well as basic microbiology. The latter concept will be useful if one decides to include the laboratory component that involves gram staining of bacteria.

Immune System Review

In addition to a standard high school Biology or college-level textbook, the following resources will be especially helpful:

- http://www.niaid.nih.gov/topics/immunesystem/documents/theimmunesystem.pdf - an online publication by the National Institute of Allergy and Infectious Diseases entitled *Understanding the Immune System: How it Works*, that provides a basic overview of immunity, as well as a glossary of terms.

- http://bcs.whfreeman.com/thelifewire/content/chp18/1802001.html - a great resource provided by the textbook publishing company, WH Freeman, that gives an excellent overview of the immune system in a tutorial animation format. This tutorial would be extremely useful for students as well.

- http://highered.mcgrawhill.com/sites/0072507470/student_view0/chapter22/animation__the_immune_response.html - an additional textbook tutorial animation

- www.depts.ttu.edu/porkindustryinstitute/.../Immunology%20**Innate**.ppt and outreach.mcb.harvard.edu/teachers/Summer04/.../Immunology.ppt – two downloadable Microsoft PowerPoint lectures that provide a good overview of immunity.

- http://www.youtube.com/watch?v=kskFjm1pKEs – a student-friendly, interesting take on the immune system as battle station. Students will greatly enjoy the metaphors used here!

- http://faculty.riohondo.edu/rbethel/videos/micro_inflammation.swf and http://www.gluegrant.org/flash/injury.swf - two flash animations covering inflammation, a key component of any immune response

- http://www.youtube.com/watch?v=rDdk0Mqkz9g – this video provides an essential review of how the innate and adaptive immune systems interact in both Cell-mediated and Antibody (or 'Humoral')-mediated immune responses

Innate Immune System Focus

Because the ultimate focus of the present curriculum is on cell communication within the innate immune system, after introducing students to the basic organization and function of the immune system, it will be important to explain how innate immune cells specifically recognize pathogens, and what role this plays in mounting an immune response.

- http://www.youtube.com/watch?v=KiLJl3NwmpU – a short video clip showing how macrophages capture microbes and release cytokines

- http://www.youtube.com/watch?v=7VQU28itVVw&feature=related – provides an animated overview of the process of *phagocytosis.*

Pathogen recognition in phagocytes of the innate immune system relies, in part on a class of membrane receptors called Toll-like Receptors (TLRs), which will be the focus of the *Practical Applications* component of this curriculum. Here are specific resources about TLRs:

- *Scientific American* is an excellent resource for a popular science perspective on a host of specific cellular processes, and an annual digital subscription to this journal, which typically

costs less than $40, is highly recommended. The following article introduces the concept of TLRs and is critical reading material for teachers wishing to use the *Practical Applications* component of this curriculum. Additionally, depending on the level of the students, it should be used as either assigned reading or lecture material: **Immunity's Early-Warning System**; January 2005; Scientific American Magazine; by Luke A. J. O'Neill; 8 Page(s).

- http://www.sinauer.com/pdf/nsp-immunity-3-10.pdf - a helpful pamphlet for teacher perusal that provides an informative overview of the TLR family of innate immune receptors

- Finally, the following animation provides an essential, and rather entertaining overview of how TLR cell-signaling results in cytokine expression, antigen presentation, and T-cell activation: http://www.youtube.com/watch?v=iVMIZy-Y3f8.

Microbiology Review

Why review this?

Because the present curriculum will end with a practical application focus on how cell signaling of TLRs plays a crucial role in innate immunity, a brief foray into the world of bacteria, with an emphasis on bacterial cell wall structure will provide specific examples of an important class of TLR ligand. Also, the laboratory component of the *Practical Applications* component includes Gram staining of bacteria.

- http://www.bacteriamuseum.org/cms/Bacteria/what-are-bacteria.html - a website offering several resources for reviewing the basics of bacteria, including types of bacteria and basic cell structure

- http://serc.carleton.edu/microbelife/research_methods/microscopy/gramstain.html - provides a basic explanation of the purpose of Gram staining.

- http://archive.microbelibrary.org/microbelibrary/files/ccImages/Articleimages/keen/Gramstainkeen.htm -an excellent animation explaining the chemistry of gram staining

Biomedical Research

A key component of the *Practical Applications* phase of this curriculum is the introduction of students to *how* immune cell signaling can be studied in a laboratory setting. Although the specific examples of this provided in the *Sample Curriculum* section are specific to an actual summer research experience studying TLR2 function in an actual immunology lab, any teacher interested in providing their own practical examples need only choose one to two primary literature articles on TLRs to be read and dissected with their students. A few specific biomedical techniques from the materials and methods section of the chosen article could then be further studied and discussed.

The following resources offer detailed explanations of some commonly used biomedical research tools in a given immunology lab:

Mammalian Tissue culture

- http://www.scq.ubc.ca/cell-culture/ - this *Science Creative Quarterly* article outlines the basic concepts underling tissue culture

- http://www.level.com.tw/html/ezcatfiles/vipweb20/img/img/20297/intro_animal_cell_culture.pdf - a great article explaining all aspects of mammalian tissue culturing methods and applications

Transfecting cells with DNA

DNA transfection involves a series of laboratory techniques used to introduce foreign DNA into a cell, and is among the most commonly used tools in biomedical research laboratories. Students who have already had a year of introductory Biology will have learned about DNA plasmids and bacterial transformation during the Biotechnology unit of the course. In mammalian cells, the technique is generally referred to as transfection and involves a similar process.

- http://www.slideworld.org/viewslides.aspx/Transfection-of-DNA-into-Eukaryotes-ppt-2022268 - This PowerPoint slide show provides an age-appropriate introduction to the concept of recombinant DNA, transfecting cells with foreign DNA and general applications. Although there are multiple ways in which transfection can be done, this slide show nicely highlights the liposome delivery method.

Fluorescence Microscopy

Most transfected DNA constructs include some sort of tag that enables researchers to confirm successful transfection and expression of the DNA. Fluorescence microscopy is an invaluable tool used to track the location of a given gene product in a transfected cell.

- http://www.invitrogen.com/site/us/en/home/support/Tutorials.html - Many biomedical supply companies offer great tutorials for a variety of topics. This invitrogen example provides a comprehensive video tutorial of fluorescence. Teachers should decide how much of the presented information to cover with students, as too many details are not necessary. A tutorial on *flow cytometry* is also included here.

Reporter Assays

Determining the activity of a given gene involved in a cellular pathway such a cell signaling can often be elucidated with the help of a reporter assay.

- http://www.promega.com/resources/multimedia/reporter-assays-and-transfection/introduction-to-reporter-gene-assays/ - this video tutorial offered by the biomedical research supply company, Promega, offers a fantastic introduction to the concept and applications of reporter assays.

Reverse Transcriptase Polymerase Chain Reaction (RT-PCR)

Because most cell signaling pathways result in the regulated expression of a gene (typically cytokine genes in the case of immune cell signaling pathways), RT-PCR provides a convenient means of quantifying the effects of receptor-ligand binding on the expression levels of downstream target genes. Students who have already taken Introductory Biology may have learned about the concept of Polymerase Chain Reaction (PCR). RT-PCR uses the basic concept of PCR to *quantify* the amount of genetic material isolated from cells. It involves isolating total cellular RNA, using the enzyme reverse transcriptase to make cDNA copies of selected mRNA transcripts of interested within the RNA sample, and quantifying this cDNA using a fluorescence-based PCR technique.

- http://www.bio.davidson.edu/people/kabernd/seminar/2002/method/lowry/RTPCR.htm - provides a useful overview of RT-PCR, as well as links to other RT-PCR websites

IV. Student Prior Knowledge and Skills

This curriculum is ideal for high school students who have already had a year of Introductory Biology, in which they were at some point exposed to basic cell structure and function, the basics of light microscopy (how to use a compound light microscope), the concept of genes and traits, and the concept of DNA, RNA, and proteins. If students meet these criteria, several components of this curriculum will provide a, still much needed review of these concepts, rather than an initial introduction to them; however, selected components of this curriculum could also be used to simply enhance either the Immunology or Cell Signaling units of an Introductory Biology course.

V. Student Outcomes and Learning Objectives

Conceptual Skills

Students will be able to:

1. Demonstrate their understanding of the basics of cell communication (reception, transduction, response) and how this process mediates a host of important physiological functions.
2. Explain in some detail, the purpose of the Immune System, as well as its structural organization into the Innate and Adaptive Immune Systems.

3. Describe the various types of leukocytes and the general concept of *cytokines* as key signaling molecules in immunity.

4. List, based on their understanding of how the innate and adaptive immune systems interact, the basic steps of an immune response, beginning with pathogen recognition by innate immune cells and ending with either a cell-mediated or humoral-mediated adaptive immune response.

5. Discuss bacteria as a specific class of microbial pathogen recognized by the immune system and explain basic bacterial cell structure, focusing on cell wall constituents.

6. Articulate in some detail the importance of Toll-like Receptors (TLRs) in mediating pathogen recognition and response by phagocytic immune cells.

7. Use popular science literature and their understanding of cell communication to explore specific TLR-mediated cell
signaling pathways.

8. Use their understanding of the Central Dogma of Molecular biology to discuss the concept of a *polymorphism* and its consequences on protein function.

9. Use the PubMed database provided by the National Library of Medicine to conduct a brief review of scientific literature pertaining to the role of TLR-2 polymorphisms in mediating immune dysfunction.

10. Explain in general terms the concepts underlying specific biomedical research tools, including cell lines, fluorescence microscopy, and realtime PCR, and how these are used in an immunology lab setting.

11. Use their understanding of cell communication and the Central Dogma to explain a specific, example of how immunologists currently seek to study TLR-mediated cell signaling in a biomedical laboratory setting.

Technical Skills

Students will be able to:

1. Use basic microbiological techniques to prepare, stain, and identify bacterial cells.

2. Explain basic hematological techniques used to identify the cellular components of blood and distinguish among various types of immune cells in a typical blood smear.

3. Articulate in general terms the practical applications of specific biomedical laboratory techniques as such as tissue culturing of cell lines, transfection of cell lines, fluorescence microscopy, reporter assays, and RT-PCR in the study of immune cell signaling pathways.

4. Navigate the scientific literature data base, PubMed in order to conduct basic primary literature research to explore the role of TLR2 signaling in mediating immune function, as well as the physiological consequences of TLR2 polymorphisms on the body's susceptibility to infectious disease.

5. Begin to develop the necessary skills involved in reading and discussing primary scientific literature.

VI. Sample Curriculum

The following is an example of the present curriculum, as it was implemented in an advanced high school Biology course elective. The entire unit lasted a total of 7 weeks, but could be paired down to last anywhere from 2 to 4 weeks, depending on the needs and desires of the teacher.

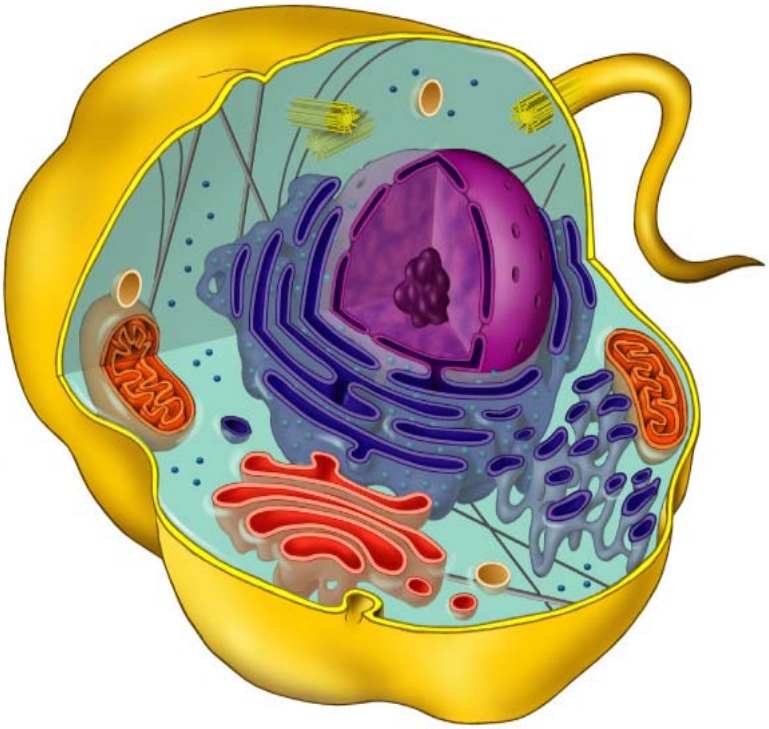
Unit I: Basic Cell Biology

Note: Homework due the first day of this unit was to read Chapter 1 of the aforementioned "Inside the Cell" publication.

Week	Topic	Curriculum Phase	Central Questions/Concepts
1	**Cell Structure**	**Introduction to key concepts**	There are over 200 types of human cells, yet all cells share similar internal structure. What is the internal structure and why is the structure similar in all human cells? Using a blank diagram of a typical animal cell, let's discuss organelle structures, functions, *and* their relative sizes. If you were commissioned to build a 3D model of a cell to scale for a museum, how would you do it?
	Central Dogma of Molecular Biology (Review)		How does information from the nucleus get translated into a functional product in a cell? What cellular compartments are involved in mediating this process? How does DNA get transcribed into mRNA? mRNA into protein? (Hemoglobin gene/protein example) What are 7 functional classes of proteins? What are mutations or polymorphisms and when can these aberrations occur along the Central dogma flow of genetic information in a cell? (Sickle Cell Allele example)
2	**Cell Communication**		What's happening at a cell's surface? Why might cellular communication be important for any given cell? What types of signals might a cell need to receive? To send? What cellular compartments are likely to be involved in cell communication? What are 3 ways in which a signal can travel to a cell? What are 4 general classes of signals?
			What are the 3 steps of cell communication? What are 4 types of receptors and how do they differ in terms of general structure, location in the cell, and type of signal they receive?
3		**Student Exploration (mini-project)**	How can we use our understanding of cell communication to explore how basic physiological processes such as sight, taste, and appetite are regulated?
4-5	**Immune system**	**Introduction to key concepts**	What is immunity? What are the major challenges facing the immune system? How is the immune system organized? What's the difference between innate and adaptive immunity, and what is the relative importance of each? What is the cell and molecular basis of immunity? How do these cellular components interact? What defines a pathogen? What are some common infectious diseases, and what do we know about the pathogens that cause them?
		Practical Applications	What does a blood smear look like? How do we distinguish among white and red blood cells? Among innate immune cells? How are bacterial pathogens classified? What do they look like?
6		**Student Exploration (mini-project)**	Exploring infectious diseases
7		**Practical Applications**	Toll-like Receptors, cell communication, and innate immunity: what are toll-like receptors, and why are biomedical research scientists interested in them? Primary Scientific literature reading and discussion: What are examples of how TLRs (specifically TLR2) are currently being studied?

Cell Biology Basics: Worksheets/Sample Assignments

A ‘typical’ animal cell



Please label the above cell diagram with the names and general functions of each compartment/structure shown. Is this diagram to scale, according to *An Owner’s Guide to the Cell*? If not, please list the sizes that each structure should be in order to be to scale (be sure to first measure the diameter of the cell)!

Diameter of cell in the above image: _____mm

Organelle/component	Function(s)	Size in diagram (mm)	Corrected size (mm)

Exploring the Central Dogma: Firefly Luciferase

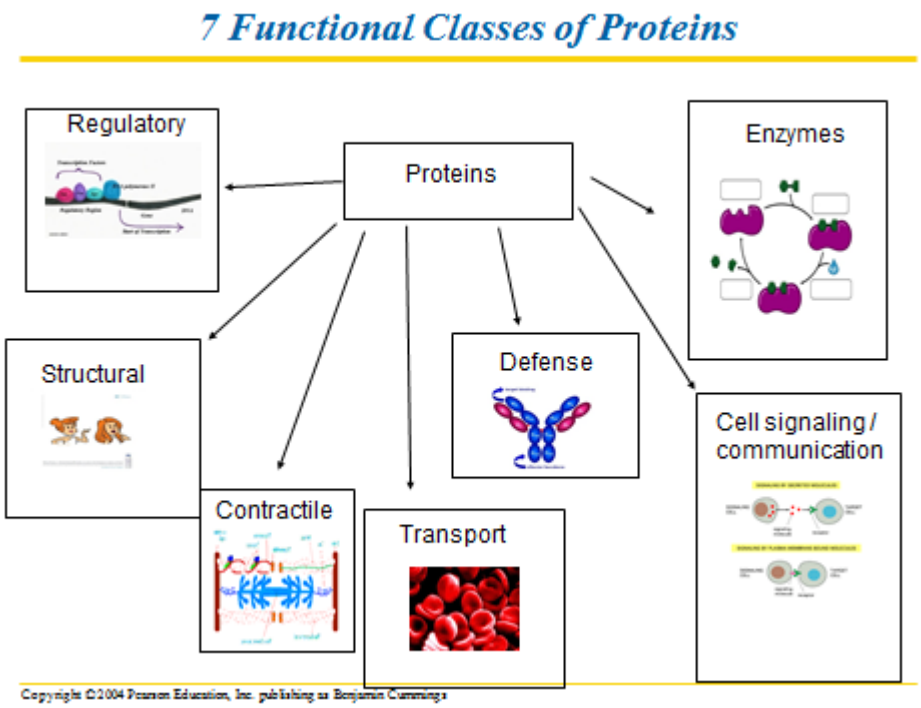
Go to this website: http://gslc.genetics.utah.edu/units/basics/

Please draw a series of simple diagrams that explain what makes a firefly glow, using all of the words below.

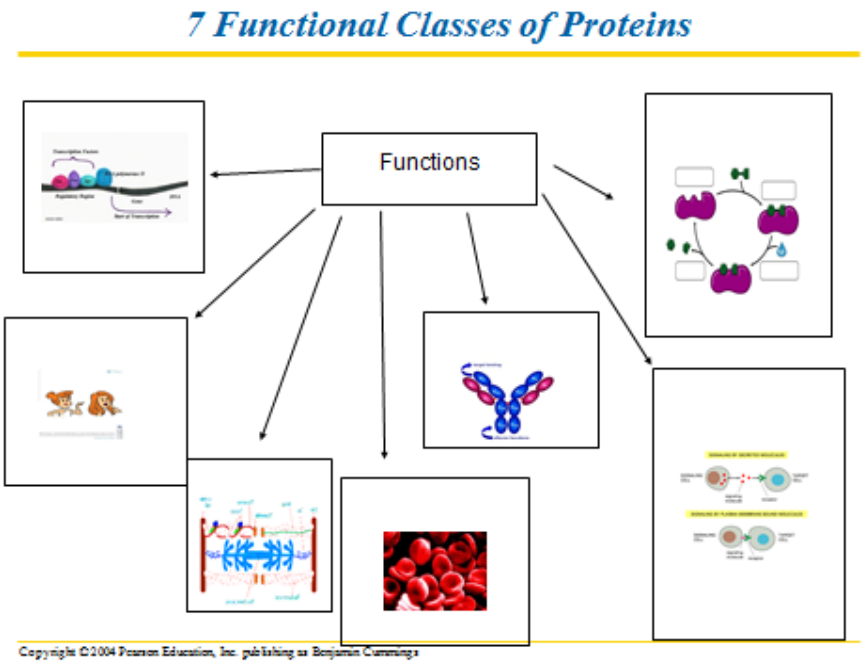
- RNA Polymerase
- LUC gene
- Transcription mRNA
- Luciferase Enzyme
- Ribosome
- Translation
- Amino Acids
- Three dimensional structure
- Luciferin
- Oxyluciferin
- Functional Luciferase Enzyme

Courtesy: http://animal.discovery.com/tv/a-list/creature-countdowns/cheats/cheats-05.html

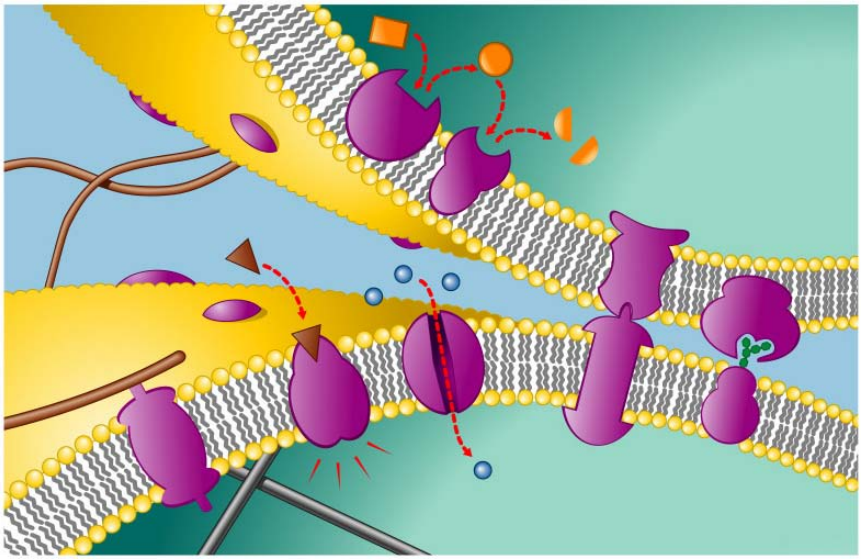
Cell Communication Basics: Worksheets/Sample Assignments



Blank version:



Life at the cell's surface



What specific cellular components do you see in this image?

Use this image to briefly describe the chemical make-up of a cell's plasma membrane.

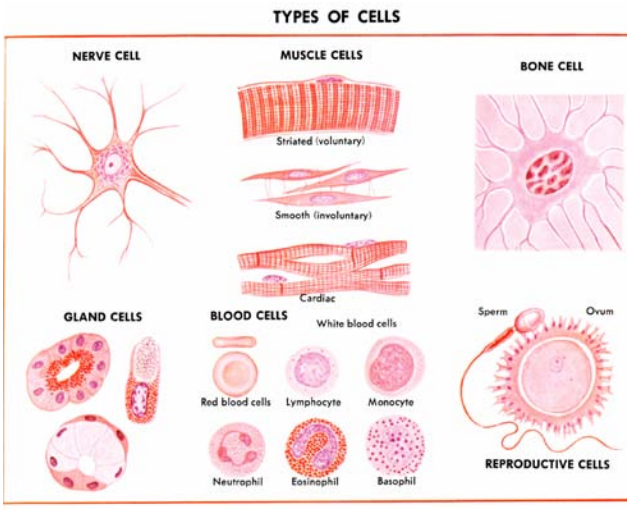
Use this image to explain the various functions of a cell's plasma membrane.

What protein functional classes do you see represented by the various plasma membrane proteins depicted in the above diagram?

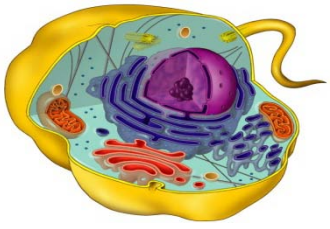
Sending and Receiving Signals

Consider the 2 diagrams below:

Why might cellular communication be important for any given cell? What types of signals might a specific cell type need to receive? To send?



How do you think a cell receives a signal?



What cellular structural components could be involved in releasing a signal? In receiving a signal? In responding to a signal?

Cell Communication Animated Tutorial Worksheet

1. Visit the following website: http://media.pearsoncmg.com/bc/bc_campbell_biology_7/media/interactivemedia/activities/load.html?11&B

2. Fill-in the following table as you navigate the tutorial:

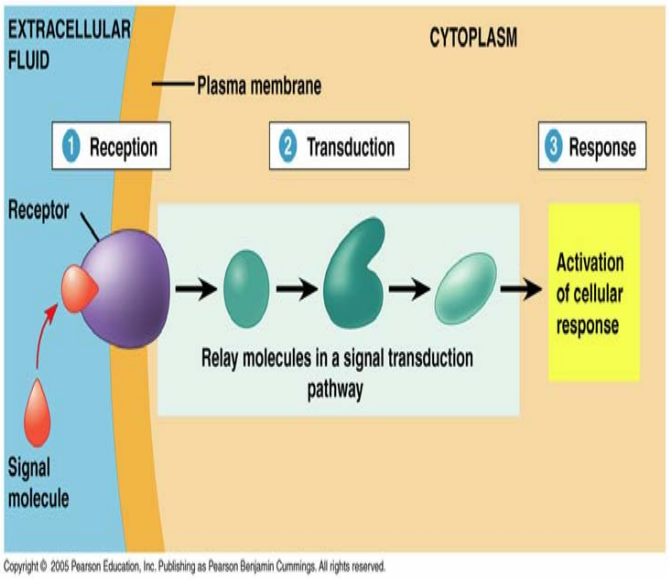
Receptor type	Rough sketch	Types of ligands	Transduction (how is information from the initial signal propagated through the cell?)
G protein-coupled receptor			
Receptor Tyrosine Kinase			
Ion channel receptor			
Intracellular receptor			

Cell Responses:

Please explain how each of the following processes is directly affected by cell communication:

Glycogen metabolism: Microtubule organization: DNA transcription:

Modeling Cell Communication



Consider the above diagram that illustrates the 3 major steps of cell communication. Please use your understanding of cell communication to ***devise a story*** using people, machines, or any other objects of your choice in which <u>various</u> messages (signals) are sent and each message results in a specific response. You may choose any scenarios you wish, but your story should include a representation of:

- two specific types of signaling (choose from: endocrine, paracrine, autocrine).
- two specific types of signaling receptors (choose from: GPCRs, RTKs, intracellular receptors, and ion channel-linked receptors).
- *how* each message is propagated (transduced) using such components as kinases, phosphatases, GTPases, and second messengers.
- specific responses that occur as a result of this message.

Cell Communication Research Project:
What? Why? How? Who? When? Where?

Now that we've covered the basics of cell communication - types of signaling mechanisms, types of signaling receptor pathways, types of ligands – you will each investigate *how cell signaling enables one of the physiological processes* listed below:

- Muscle contraction
- Taste
- Appetite/metabolism (leptin)
- Appetite/metabolism (insulin)
- Growth
- Puberty (testosterone)
- Smell
- Sight

Your task: Use the internet to learn about the role cell communication plays in facilitating your chosen physiological process by putting together a *brief* PowerPoint slide show (no more than 5 -7 slides). Your PowerPoint must contain the following information:

1. What type of signaling is involved (paracrine, endocrine, autocrine, synaptic)?
2. What type of cell is secreting the ligand? (What is the name of this cell type, and where in the body is this cell found?)
3. What is the name of the ligand, and what type of ligand is it (hormone [which type], neurotransmitter, lipid, etc.)?
4. What cell type is the target for this ligand (Where in the body is this cell type found?)
5. What is the name of the receptor involved?
6. What type of receptor is it (G-protein-coupled, RTK, ion channel-linked, intracellular?)
7. What are the cellular outputs of this signaling; *i.e.*, how does the target cell respond?

Wherever you can, please include images that portray at least 5 out of the 7 points above. You will present your PowerPoint to the class so that the table on the next page can be filled-in. Your presentation should last approximately 10 minutes.

Cell Communication

Key Terms/Concepts

Membrane protein	Eicosanoids	Gap junctions
Hydrophobic	Neurotransmitters	Phosphorylation / dephosphorylation
Hydrophilic	Paracrine signaling	Kinase / phosphatase
Reception	Endocrine signaling	G protein-coupled receptor
Transduction	Synaptic signaling	Receptor Tyrosine Kinase
Response	Autocrine signaling	Ion channel receptor
Receptor	Cascade	
Ligand	Second messenger	
Hormone	Amplification	

Our questions:

1. What are the major functions of the plasma membrane of any given cell?
2. What is the lipid and protein make-up of the plasma membrane and how does this make up enable it to perform its various functions?
3. Why is cell communication so important?
4. What is a ligand and what are some categories of ligands?
5. What are the 4 major ways in which a signal can travel to a cell (what do we mean by local vs long distance signaling)?
6. What are 3 properties that all cell signaling receptors have, regardless of whether they are membrane or intracellular receptors?
7. What are some differences between G protein-coupled receptors and Receptor Tyrosine Kinases?
8. What cellular components/organelles are involved in cell communication?
9. What is phosphorylation? What special class of cellular molecules carries out this chemical reaction, and what are its uses in cell communication?
10. What is dephosphorylation? What special class of cellular molecules carries out this chemical reaction, and what are its uses in cell communication?
11. How does cell communication lead to any TWO of the following physiological processes : taste, sight, muscle contraction, appetite, growth (cell division), sperm cell maturation?

Immune System
Worksheets/Sample Assignments

Immune Response Mechanisms

Cell-mediated Immune Response

Order the following in chronological order by placing the appropriate number next to each one (starting with "1."

___T_H cells multiply.

___Macrophages engulf and digest foreign invaders.

___T_c cells bind to macrophages.

___T_c cells target and trigger apoptosis in infected cells.

___Macrophages present portions of foreign substances on their cell surfaces.

___T_H cells bind to and get activated by macrophages.

___T_c cells multiply.

___T_H cells activate T_c cells.

Antibody-mediated response

Order the following in chronological order by placing the appropriate number next to each one (starting with "1."

___B cells recognize specific foreign invaders.

___Macrophages engulf and digest foreign invaders.

___Macrophages present portions of foreign substances on their cell surfaces.

___B cells become 'Plasma Cells' and secrete antibodies.

___T_H cells bind to activated B cells and cause them to proliferate.

___B cells become 'Memory Cells.'

___T_H cells bind to and get activated by macrophages.

___Antibodies bind to foreign invaders and target them for destruction.

Comic Strip Assignment Option 1:

Defense and the Immune System / Infectious Disease

You may work with a partner for this assignment. As you learned from your reading, there are many cells that participate in fighting invasion by foreign substances. Working in groups of two, your task is to create a comic strip that depicts what an immune response *might* look like if a person were infected with the pathogens listed below and was somehow able to beat the infection.

Include in your comic strip:

A profile of the pathogen – simple drawing, main features, where it can be found in the environment, how it enters the body

A brief description of the disease it causes – signs, symptoms, treatment

A step-by-step scenario that shows how certain immune cells might react to the pathogen.

Pathogen #1: *Streptococcus pyogenes*

Illness caused: Scarlet Fever

Pathogen #2: Clostridium tetani.

Illness caused: Tetanus

Comic Strip Assignment Option 2:

Immune Response Comic Strip Project

Create a comic strip containing **a minimum of 8 panels** in which you devise an imaginary scenario that leads to an immune response in the body. All three lines of defense must be involved.

Your comic strip must demonstrate the actions/role of the following components:

- Three distinct granulocytes of your choice
- Toll-like Receptors (TLRs) (use of specific TLRs would be ideal)
- 1st line of defense
- T lymphocytes (use two specific types)
- B lymphocytes (be specific)
- Antibodies (extra credit: a specific antibody isotype is used (IgG, IgM, IgD, IgE, IgA)
- Cytokines (please use at least 2 distinct cytokines)
- Phagocytosis
- Inflammation
- Antigen

Your comic strip must address the following concepts:

- Three or more challenges that the immune system must face and how it meets these challenges
- How the innate and adaptive immune systems communicate
- What is meant by the statement that the immune system is cell-based, protein-based, and mobile
- How B cell and T cell functions/actions differ from one another

Your comic strip must have:

- Dialogue
- drawings

You will be graded on:

- your descriptions' accuracy of how the immune response works
- the level of detail you use in your drawings and descriptions and your ability to include as many terms discussed in class as possible (as they relate to your chosen scenario)
- clarity of the action/role of each component
- your ability to include all listed components in the comic strip
- your ability to address all required concepts in the comic strip

Good Luck!!

Cell Biology of the Immune System

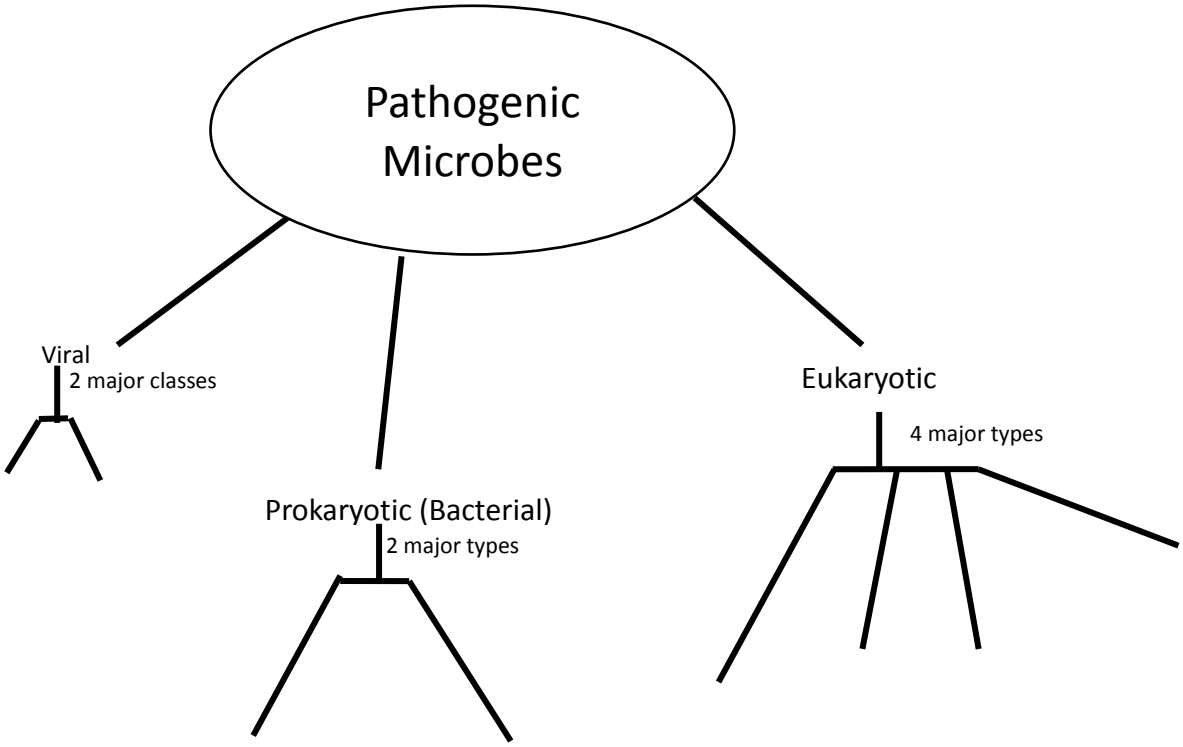
Key Terms/Concepts

Blood	cytokines	plasma cell
Blood types/ groups	eosinophil	humoral immunity
MHC molecules	basophil	antibodies
Erythrocytes	granulocyte	monoclonal/polyclonal antibodies
platelets	agranulocyte	antigen
macrophage	lymphocyte	T Cell (helper, cytotoxic)
neutrophil	B Cell	Cell-mediated immunity
phagocyte/phagocytosis	clonal selection	histamine
toll-like receptors	self tolerance	mast cells
inflammation	memory cell	

Our questions:

1. What is the immune system, and where can it be found in the body?
2. How, in general, does the immune system determine what is 'self' and what is 'non-self' (foreign)?
3. What are the roles of the innate immune system?
4. Describe the cellular components of the innate immune system.
5. Please describe the general mechanism of inflammation? How can too much inflammation be dangerous for the body?
6. Why is cell communication important in immunity?
7. What are Toll-like Receptors, and why are they important in mediating immunity?
8. Describe the localization and general role of any three Toll-like receptors (including TLR-2) in a given macrophage cell.
9. What are cytokines, and what role do they play in immunity?
10. What are the roles of the adaptive immune system?
11. What are the general mechanisms by which the innate immune system interacts with the adaptive immune system?
12. Describe the cellular components of the adaptive immune system.
13. How is the *cell-mediated response* different from the *humoral response*?

Use the Internet to research the major types of pathogenic microbes, and use this information to complete the concept map below. Provide specific examples of microbes for each subcategory and the infectious disease they cause.



Pathogen Wanted Poster

Small Pox	Anthrax
Typhoid fever	Malaria
Syphilis	SARS
Bubonic Plague	Ebola
Cholera	HIV/AIDS

Choose one of the above infectious diseases to study and to create an 8 ½ x 11 sized wanted poster about the microbe that causes the disease. Find out the following:

Microbe involved (include its common name, scientific name, and an image)

Where is this microbe usually found (geographically)?

How the infection is acquired

Signs, symptoms of infection, ultimate result of infection (include images)

Current Treatments (public health practices, drugs)

Immunity's Early Warning System Article Worksheet: Components of the Immune System

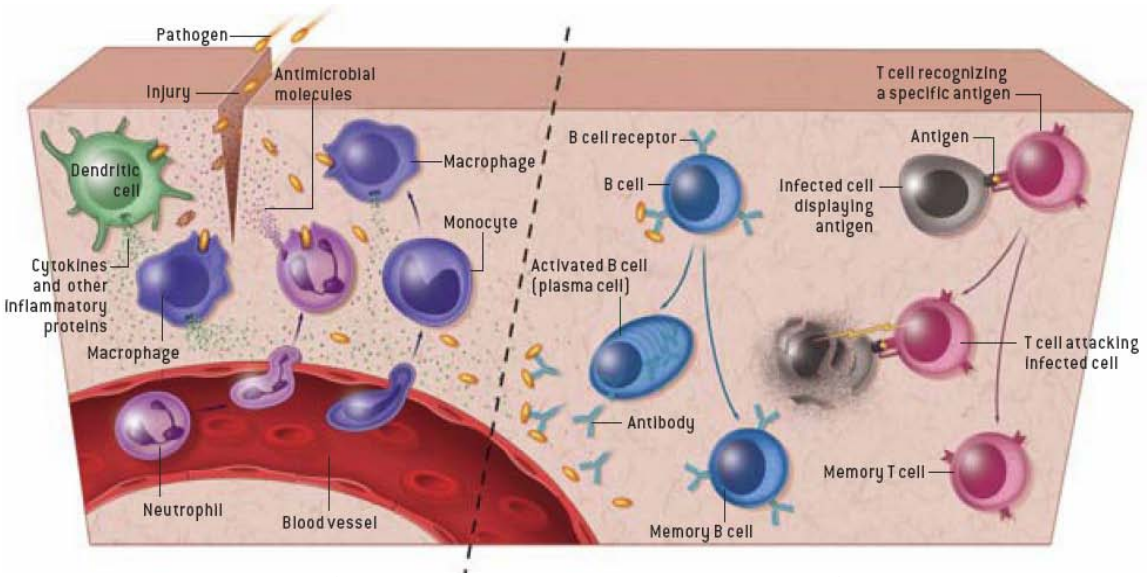


Image adapted from: L.J. Oneil (2005). *Immunity's Early Warning System. Scientific American*

1. Please use the image above to do the following:

   a) On the appropriate side of the dotted line above, label the diagram with 'Innate Immune System' and 'Adaptive Immune System'.

   b) List 3 differences between innate immune cells and adaptive immune cells.

   c) Provide a brief description of what is happening on the Innate Immune System side of the diagram.

   d) Provide a brief description of what is happening on the Adaptive Immune System side.

Immunity's Early Warning System Article Worksheet: Toll-like Receptors

1. Briefly explain the role that toll-like receptors play in innate immunity.

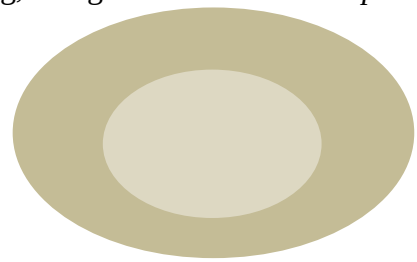
2. In the box to the left below, sketch the basic structure of a plasma membrane toll-like receptor, and label its extracellular, transmembrane, and intracellular (cytosolic) regions.

3. In the box to the right below, sketch the basic structure of an endosome toll-like receptor and label its extracellular, transmembrane, and lumenal (the portion that would be inside the endosome) regions.

4. What types of ligands do plasma membrane TLRs recognize? What about endosome TLRs?

5. Why have endosome TLRs?

6. Use the diagram of a cell and its nucleus below to depict how cell signaling works with Toll-like Receptor 4 and its lipopolysaccharide (LPS) ligand. Write a brief explanation for what's happening, being sure to include *reception*, *transduction*, and *response*.



Reading Primary Literature

The following questions are adapted from *Cell Biology For Life* (Garland Science Publishing www.garlandscience.com/cbl).

As you read your first assigned primary literature article, please jot down answers to the following questions. You should feel free to write directly on the article. Circle what you believe to be key words, phrases, or sentences that might help you answer each question.

1. What can you learn from the title of the paper?

2. Who are the authors and what agenda might they have?

3. Does the abstract draw a big picture and clearly state the question, hypothesis, experiments and results? If so, state them in your own words.

4. What parts of the paper do you find most intimidating or difficult to understand? How did you deal with this? What if any outside sources did you find yourself using as you read through these parts?

5. What parts of the paper do you find most interesting? Why?

6. What can you learn from the figures? Please state the information here in your own words.

7. What are the dependent and independent variables in the assays? What appear to be negative and positive controls and how do they appear useful?

8. Is the data convincing? Why or why not?

9. Summarize the authors' conclusions.

10. Summarize the paper in your own words.

11. If you could write an alternative title for this paper in your own words that described its goals and accomplished objectives, what would it be?