LEARNING GOAL
You will be able to explain how TLR, MHC & DC dictate the type of immune response and then how T-cells orchestrate them.

OBJECTIVES
To achieve this goal, you will have to be able to:
• Differentiate T-cell functions.
• Understand how cytokine profiles interact with T-cell subsets to produce appropriate responses to pathogens.
• Explain how deficiency of Th-1 function can cause disease.
• Explain the clinical consequences of the Th-2 reaction.

BACKGROUND READING
Janeway 7th edition: 359-360 (do not even think of memorizing table 8.34); 505-506 and posted article

DEVELOPED BY
John A. Robinson, MD
HOW TO SUCCEED IN SMALL GROUPS

Before coming to class:

1. Read assigned chapters/pages and develop answers for **ALL** the questions in the 4 clinical vignettes

During the Small Group Session:

2. Each small group (**should be 4-5 peers**- **please do not sort yourselves into large groups-you will learn much less**) should discuss the four case studies and decide the best solutions to the specific integrating questions associated with each case.

3. After approximately an hour of discussion by the subgroups, the facilitator will recapitulate the answers to the integrating questions by selecting a subgroup to present a synthesis of their relevant discussions to the entire group. Facilitators will select, at their discretion, a small group for the discussion of the individual cases.

4. History has shown that students who don’t contribute to the Small Groups do not do well in the Course (remember that about 25-30% of the final comes from small groups!) and also have been assaulted by their fellow group members

5. At the end of the session, a master answer sheet will be posted on the Host Defense website.
CASE 1

Leprosy is caused by a mycobacterium related to the organism that causes tuberculosis. The disease has two major forms of expression. One, the tuberculoid form, is characterized by localized granulomas (clusters of macrophages, T cells, DC and necrotic debris). These patients are capable of mounting a normal Th1 response to the infection. The other form, lepromatoid, is characterized by widespread infection, sparse cellular reactions in the organs involved and a poor prognosis. These patients are incapable of mounting a Th1 response to the organism.

1. Why don’t all patients infected with M. Leprae manifest similar clinical states? How does the journal article assigned for this small group help explain the different disease manifestations?

2. On occasion, patients with one form of leprosy will convert to the other-how could this happen and how could it be detected immunologically?

3. Clinicians must be aware of the potential dangers and benefits associated with therapy that influences T-cell expression. Discuss mechanisms of action, cytokines influenced, and the advantages and pitfalls of the use of corticosteroids in leprosy patients. Clinical examples: a pineapple picker in Hawaii develops numbness and paralysis in his right hand. Physical examination reveals a single, well localized mass in his right axilla which, upon biopsy, reveals leprosy organisms and marked inflammation in and about the nerves of the brachial plexus. Another patient has three small skin nodules but no symptoms and these are also positive for leprosy. Which pineapple picking patient might benefit the most from the use of medications that suppress Th1 reactions?

4. If you wanted to develop a vaccine against leprosy, what cytokine gene(s) could be added to a living but attenuated leprosy preparation in order to mimic an actual infection?

CASE 2

Diphtheria is a bacterial infection that exerts many of its clinical effects by production of soluble protein exotoxins that circulate in the blood and damage the peripheral and cranial nervous system. What strategies should dictate the development of a vaccine for this disease?

1. What type of T-cell responses must be evoked and why?

2. What should be the characteristics of the antigens in this type of vaccine?
3. The toxoid can bind to nerve conducting tissue in the heart. If a patient with this infection develops abnormal ventricular conduction detected by an EKG, what immunologic strategy, in theory, might be life saving?

4. If toxoid proteins were made for a vaccine but it was discovered that they couldn’t evoke the cytokine profile necessary for a successful vaccine, what genes could be added to the protein antigens to make it effective?

CASE 3
Four infants from the same small isolated mountain village died from disseminated infection with Bacillus Calmette-Guerin (BCG). BCG is an attenuated, living tubercular bacillus used extensively for vaccination against mycobacterial tuberculosis in European and Asian countries. All 4 children had a fulminating (rapidly progressive) systemic illness characterized by fever, sweats and weight loss. Two were sisters whose parents were first cousins; the third was related to the sisters as a fourth cousin through both parents. The fourth patient has no known link to the other three. The first cousin parents were healthy and had received BCG in the past, and had four other healthy children, all of whom had received BCG.

1. Discuss the possible epidemiologic reasons and, in order of probability; discuss likely points in the immune response for a genetic defect that would lead to this type of immuno deficiency.

2. Design experiments that would support your hypothesis that it may be a genetic defect and identify the actual defect.

3. Design strategies to correct the defect.

4. There has been extensive clinical use of monoclonal antibodies that block TNF-α in patients with autoimmune diseases like rheumatoid arthritis. If one of these patients developed rheumatoid arthritis, a disease mediated by TNF-α, would a creative clinician want to try them here?

CASE 4
4A. In October 2001 (this is almost a true story), enthusiasts from 30 countries attended the world championship of model airplane flying held at Lost Hills, CA (in the central valley)[up to this point, completely true] Two weeks later, after returning home, 27 of the participants developed flu-like symptoms characterized by fatigue, fever, mild joint pains and muscle aches. Chest x-rays were done in 12 and at least half of this group had bilateral pulmonary infiltrates. One patient required admission to intensive care.
Epidemiologic analysis did not detect any specific activity or condition common to the group other than travel to CA and flying model airplanes in very dusty conditions. There was no clinical evidence in any of the patients of prior immunosuppressive therapy or immune defects. All the patients had serologic evidence of recent *Coccidiomycosis* infection (a fungus with an infectious form that lives in the soil).

4B. A large group of intravenous drug abusers shared a needle for heroin injection. Fortunately none of them were HIV positive but, unfortunately, one was an asymptomatic Hepatitis B carrier. Four months later, 2 of the drug abusers were dead from fulminant hepatitis B, 6 were recovering from clinical hepatitis.

1. Why was there a broad spectrum of disease expression in both the model plane flyers and the drug abusers?

2. Describe the defective or missing component of the immune response in the patient in the ICU and the three patients that died from hepatitis.

3. Postulate ways that you could convert the carriers to a non-infectious state.

4. One of the patients with fulminant liver disease had an identical twin that is a dialysis technician and had been previously immunized with the Hepatitis B vaccine because of the occupational hazard. Devise creative ways that a physician could have exploited this stroke of luck.