Vermont Veterinary Medical Association

2025
Winter CE Conference

February 1 and 2

Dr. Amelia Woolums
DVM, PhD, DACVM
Mississippi State University College of Veterinary Medicine

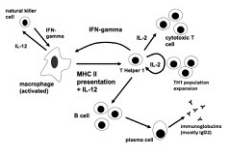
Amazing Immune Response

Generously sponsored by:

DIPAOLA

Antech®
Smarter Diagnostics. Better Care.

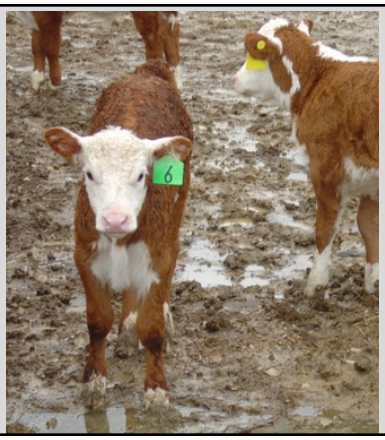
The Amazing Immune Response: Review and Update



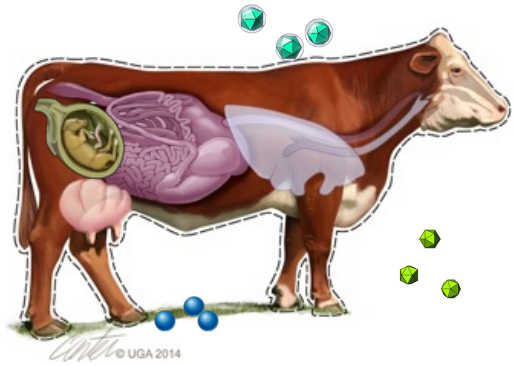
Amelia R. Woolums, DVM MVSc PhD DACVIM DACVM
Department of Pathobiology and Population Medicine
Mississippi State University
amelia.woolums@msstate.edu

MISSISSIPPI STATE UNIVERSITY – COLLEGE OF VETERINARY MEDICINE

1



2



3

Immune System: Overview

- Innate immune response
  - Immediately and always active
  - Responds to a broad variety of agents
- Acquired (aka adaptive) immune response
  - Takes several days-weeks to be fully active
  - Reacts specifically to a single agent
  - Improves with repeated exposure: "memory"
  - Target of vaccination

MISSISSIPPI STATE UNIVERSITY – COLLEGE OF VETERINARY MEDICINE

4

Immune System: Overview

- Innate and acquired responses are active in 2 major sites
  - mucosal surfaces
  - blood and tissue fluids
- Host is thus protected from attack on any front

MISSISSIPPI STATE UNIVERSITY – COLLEGE OF VETERINARY MEDICINE

5

Innate immune system: components

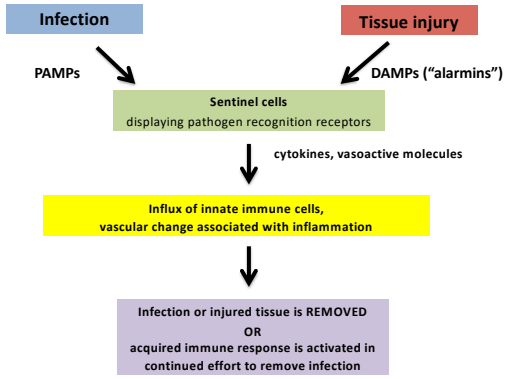
- Physical or chemical barriers
  - Skin, mucociliary elevator, gastric pH, urine flow
- Soluble factors
  - in serum, secretions, excretions, tissue fluids
- Cellular factors
  - granulocytes, macrophages, natural killer cells, gamma delta T cells, epithelial cells

MISSISSIPPI STATE UNIVERSITY – COLLEGE OF VETERINARY MEDICINE

6

- Mechanisms important in the initial response to infection are also involved in the response to non-infectious tissue injury
  - trauma
  - burns or frostbite
  - bites
- All induce inflammation
- Inflammation activates the immune response

7



8

PAMPs and PRRs

- PAMPs: pathogen associated molecular patterns
  - Highly conserved molecules found in many different microorganisms
  - Host response evolved to recognize these
    - relatively few molecules can initiate immunity to the limitless microbial world

9

Important PAMPs

- Peptidoglycan and lipoteichoic acid
  - Gram positive bacteria (Staph., Strep., and others)
- Lipopolysaccharide
  - Gram negative bacteria (E. coli, Salmonella, and others)
- Glycolipids
  - acid-fast bacteria (mycobacteria: Johne's disease, TB)
- Mannan-rich carbohydrates
  - fungi (Aspergillus and others)
- Unmethylated CpG nucleotide motifs
  - bacteria and viruses
- dsRNA
  - viruses

10

Some important DAMPs

- DAMPs are components of host tissues
- **Extracellular** DAMPs
  - Extracellular matrix components
    - hyaluronic acid
    - fibronectin
    - collagen-derived peptides
    - elastin
- Release of small and/or soluble fragments during tissue injury allows PRR activation

11

- **Intracellular** DAMPs
  - High mobility group box protein-1 (**HMGB1**)
    - Associated with DNA in normal cells: ensures proper folding
    - Triggers inflammation when released from damaged cells
      - If DNA associated: anti-DNA response can occur
    - Can be secreted by macrophages
  - Unmethylated CpG DNA **from mitochondria**
  - Adenosine
    - In cAMP, ATP, nucleic acids
  - Uric acid
    - Breakdown product of purines (e.g. adenine, guanine)

12

- Sentinel cells in tissues are the first cells to "see" PAMPs or DAMPs
  - dendritic cells
  - macrophages
  - mast cells
  - epithelial cells
  - fibroblasts

These cells can also be called into regions of inflammation

13

Macrophages

- Identify and kill pathogens via many PRRs and other surface receptors
  - phagocytosis
  - secrete antimicrobial products
- Produce proinflammatory cytokines
  - IL-1, TNF-α, and IL-6
  - activate inflammation
    - kick off the immune response

14

- Given stimuli that lead to "classical activation", macrophages become **M1 macrophages**
  - Phagocytosis
  - Microbial killing
  - Proinflammatory cytokine production
- Given stimuli that lead to "alternative activation", macrophages become **M2 macrophages**
  - Suppression of inflammation
  - Promotion of blood vessel formation
  - Promotion of tissue remodeling and repair

15

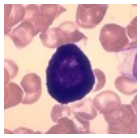
"Accumulated evidence indicates that macrophages are functionally plastic cells with the potential to alter their activities progressively and reversibly in response to changes in the tissue environment."

Sang et al., 2011

16

Mast Cells

- Mucosal mast cells: under mucosal surfaces
- Connective tissue mast cells: in skin, peritoneal cavity
- Granules contain enzymes and vasoactive mediators
- Degranulation mediated by IgE
  - **Key mediator of allergy and anaphylaxis**



17

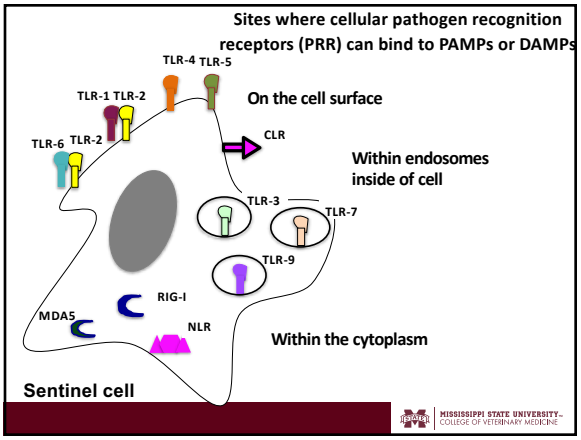
- New information: mast cells can respond to PAMPs and DAMPs via PRRs
  - Help initiate early inflammatory response to many stimuli
  - Granules are released "piecemeal"
    - Provides a more titrated response than IgE-mediated degranulation

18

Pathogen recognition receptors (PRR)

- Sentinel cells activate inflammatory/immune response when their PRR bind PAMPs or DAMPs
- PRR are found
  - On cell surface
  - Inside endosomes inside the cell
  - In cell cytoplasm

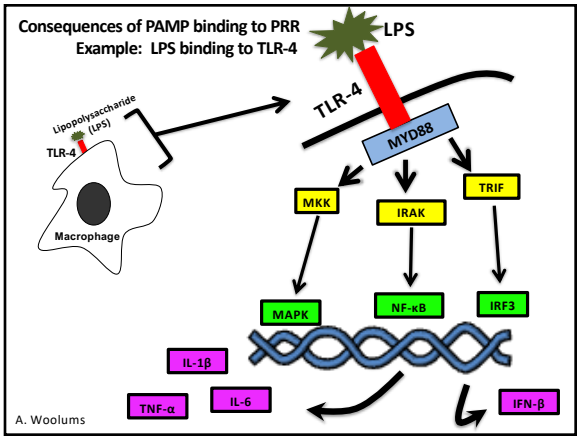
19



20

- Binding of PRR by a PAMP or DAMP initiates a signal transduction sequence in the cell
- Cell produces cytokines that activate the inflammatory/immune response
- Mixture of cytokines produced determines the kind of immune response activated

21



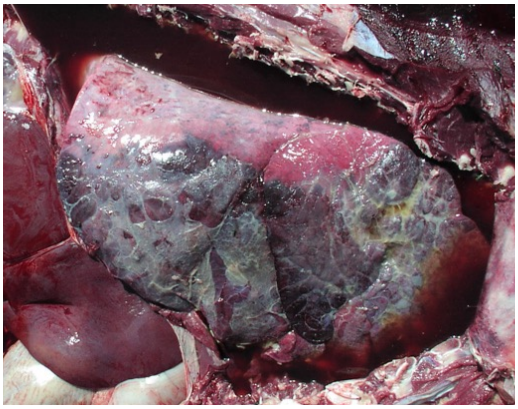
22

Cytokines

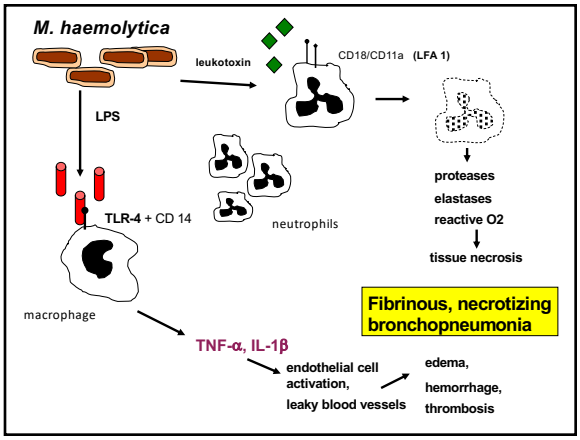
- All cells influence other cells by release of cytokines
- Cytokines...
  - Activate the immune response
  - Direct specific types of responses
    - Anti-viral, anti-bacterial, anti-parasitic
  - Contribute to inflammation and sometimes death
    - "Septic shock"

23

24

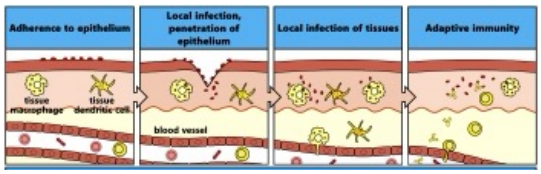


25



26

Other Players in the Innate Immune Response

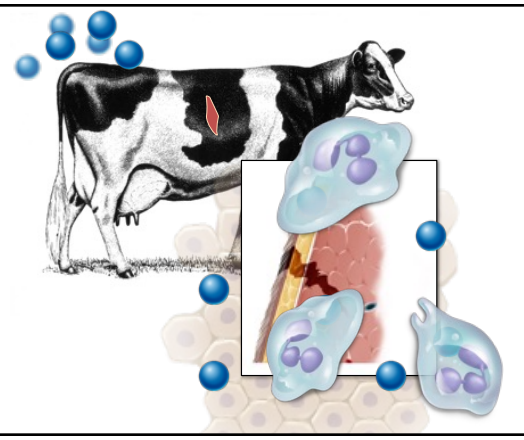


27

Innate immunity, soluble factors

- Defensins and cathelicidins
  - kill or inactivate bacteria, fungi, enveloped viruses
- Lysozyme
  - degrades peptidoglycan
- Lectins
  - bind microbial carbohydrates (e.g., to opsonize)
- Iron-binding proteins
- Complement

28



29

- Soluble factors are not only antimicrobial
- Some also activate immune cells
  - act as "natural adjuvants"
  - a cathelicidin included in an experimental vaccine improved immune responses in cattle

Kovacs-Nolan et al., 2009

30

Innate immunity, cells

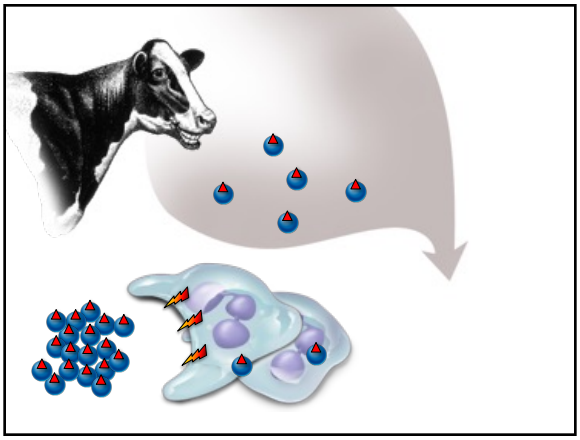
- Granulocytes: immediate responders
  - Neutrophils: any infection or injury
  - Eosinophils: parasites and hypersensitivity
    - New info: can also be immunoregulatory
  - Basophils: functions not well characterized

31

Neutrophils

- "First responders"
  - Among the first immune cells to come to site of infection
- Mediate anti-pathogen defense
  - Engulf (phagocytose) and destroy pathogens with
    - reactive oxygen species (ROS) via the respiratory burst
    - proteolytic enzymes
    - antimicrobial peptides

32

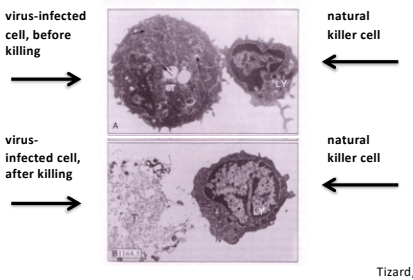


33

Natural killer cells

- Major mediator of innate anti-viral defense
- Large, granular, nonphagocytic lymphocytes
- Respond to balance of inhibitory and activating signals on target cells
  - MHC I on healthy cell: inhibitory signal transmitted
  - Lack of MHC I: activating signal
- Also produce soluble antimicrobial factors

34



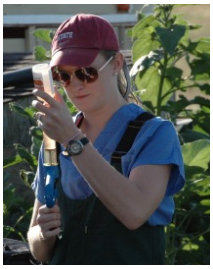
35

Gamma Delta ($\gamma\delta$) T cells

- "In between" innate and acquired immunity
- Can be active immediately
  - Produce cytokines, kill other cells, **survey mucosa**
- Also exhibit some memory
  - Improved response following some vaccines
- Gamma delta T cells make up major proportion of circulating cells in young ruminants and swine
  - Significance?

36

Acquired Immune Response



37

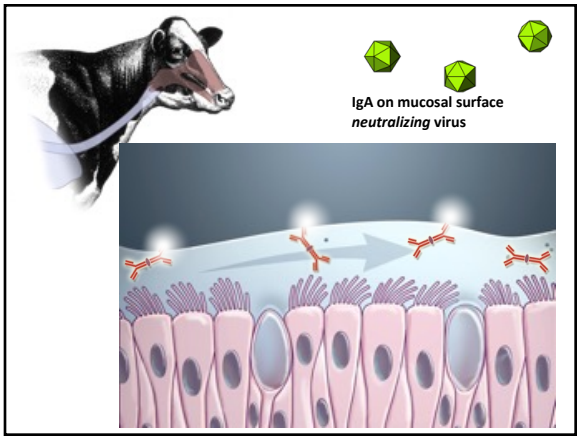
Acquired Immune Response

- Soluble factor: ANTIBODY
  - Binds specifically to foreign substances
  - Produced by B lymphocytes and plasma cells
  - Immunoglobulin classes
    - IgM: multivalent, produced first
    - IgA: mucosal surfaces (respiratory, gut, mammary gland)
    - IgG: serum, colostrum
    - IgE: anti-parasitic, mediates allergy

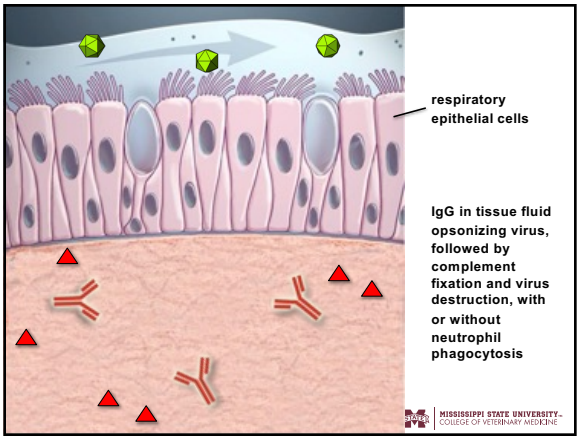
38

- On mucosal surfaces, antibody binds to pathogens and prevents pathogen entry
  - This is neutralization
- In tissues, antibody binds to pathogens and then
  - Complement is fixed: pathogen is killed OR
  - Neutrophil or macrophage binds antibody and phagocytoses pathogen OR
  - Neutrophil, macrophage, or NK cell bind antibody and kill pathogen

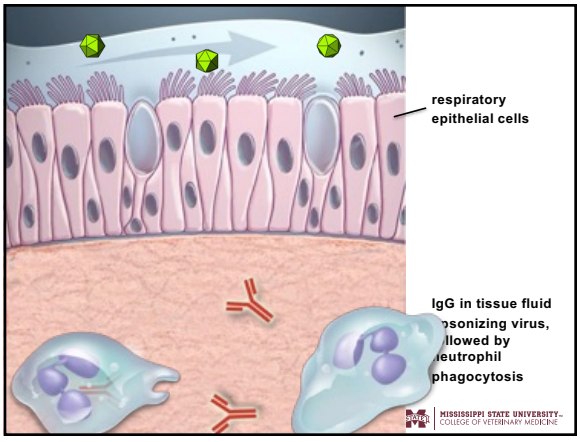
39



40



41



42

Acquired Immune Response

- Cells
  - B cells: produce antibody
  - T cells
    - Cytotoxic T cells (CD8-bearing)
      - Kill infected cells, tumor cells
        - » Viral immunity
        - » Intracellular infections
    - Helper T cells (CD4-bearing)
      - Modify responses of other cells

43

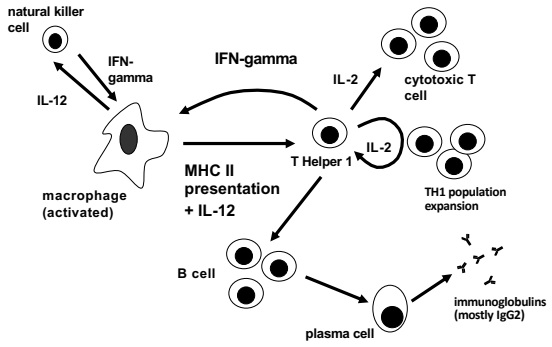
- Different types of helper T cells stimulate different types of immunity
  - T helper type 1 (TH1): intracellular infections
    - Viruses
    - TB, Johne's, *Salmonella*
    - In general, strong cell-mediated immunity
  - T helper type 2 (TH2): extracellular parasites, bacteria
    - Nematodes, flukes, ticks
    - Extracellular bacteria (*E. coli, Mannheimia*)
    - In general, strong humoral immunity (especially IgG1 and IgE)

44

- TH1 and TH2 responses are (somewhat) mutually exclusive
  - Strong TH1 → weaker TH2
  - Strong TH2 → weaker TH1
- Infections early in life may impact response to other types of infection later?

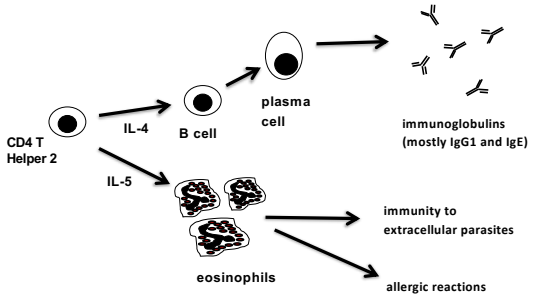
45

Interactions important in defense against viruses and other intracellular pathogens: TH1-mediated "cell mediated immunity"



46

Interactions in TH2-mediated defense against extracellular parasites and bacteria, and allergic reactions



47

TH17 cells

- CD4 helper cells that secrete IL-17 and IL-25
  - induce epithelial cells and fibroblasts to produce chemokines
  - chemokines call in neutrophils
- In people: associated with some autoimmune and chronic inflammatory diseases
- Helpful in defense against extracellular bacteria and fungi

48

Regulatory T cells ("Treg")

- CD4 helper cells that modulate or decrease the functions of other T cells
- Necessary to bring the immune response to a close after infection has been cleared
- In people: defects in Treg function associated with chronic inflammatory or auto-immune disease
- In cattle: may play a role to influence disease severity
  - e.g., in BVDV infection

49

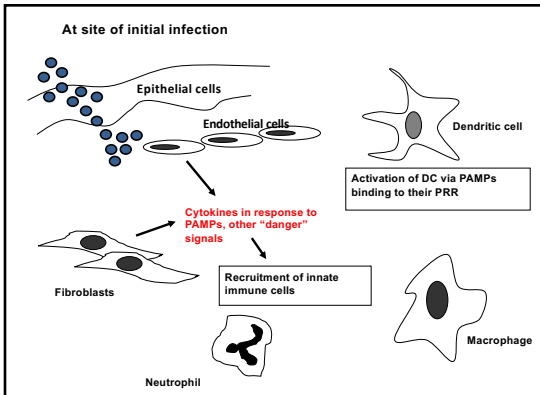
- T cells cannot respond to infection alone
- Must be shown that there is an infection by antigen presenting cells (APC)

50

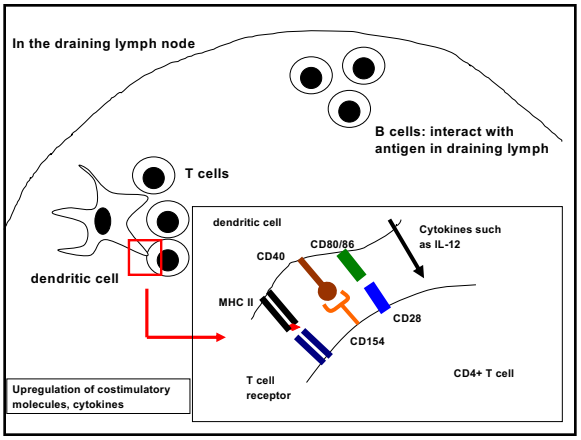
Antigen presenting cells (APC)

- APC activate T cells
  - "Show" them antigen
  - Stimulate them to respond, proliferate
- Dendritic cells control development of T helper cells

51



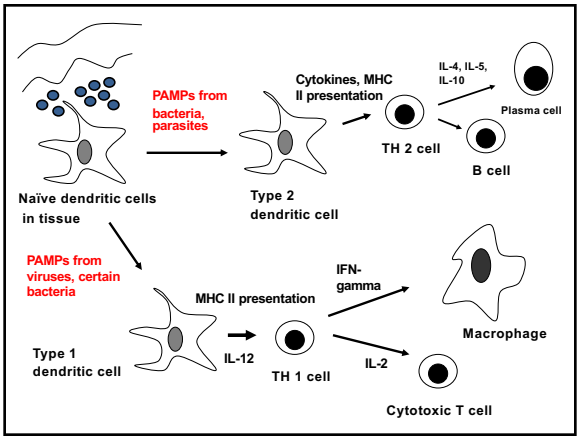
52



53

- The interaction between the dendritic cell and naïve T helper cell determines the future of the T cell
- The T cell may become a:
  - **T helper type 1** cell (TH1)
    - effective immunity to viruses and intracellular bacteria (cell mediated immunity)
  - **T helper type 2** cell (TH2)
    - effective humoral, mucosal and anti-parasite immunity
  - **T helper type 17** cell (TH17)
    - effective neutrophil responses: immunity to bacteria
  - **T regulatory cell** (Treg)
    - modulate or suppress other T cell responses

54



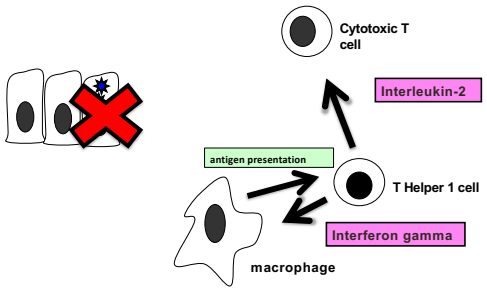
55

- Influencing the interaction between dendritic cells and naïve T cells is currently a major focus of vaccine research

MISSISSIPPI STATE UNIVERSITY – COLLEGE OF VETERINARY MEDICINE

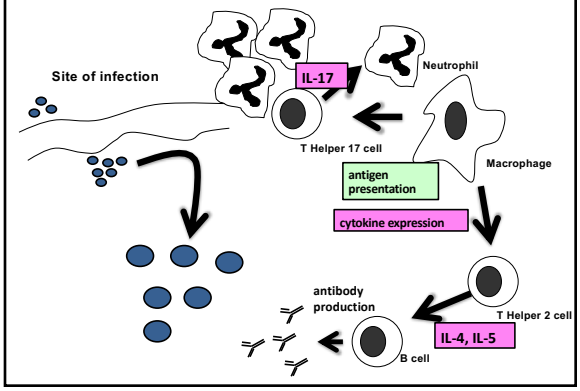
56

Major players in effective immunity to viruses



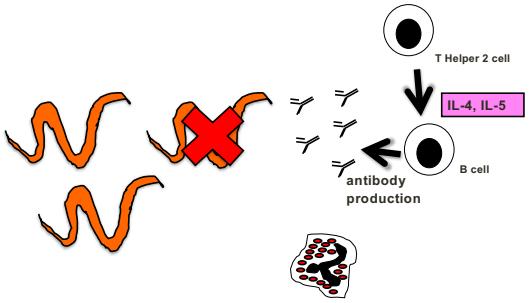
57

Major players in effective immunity against bacteria



58

Major players in effective immunity to nematodes



59

60