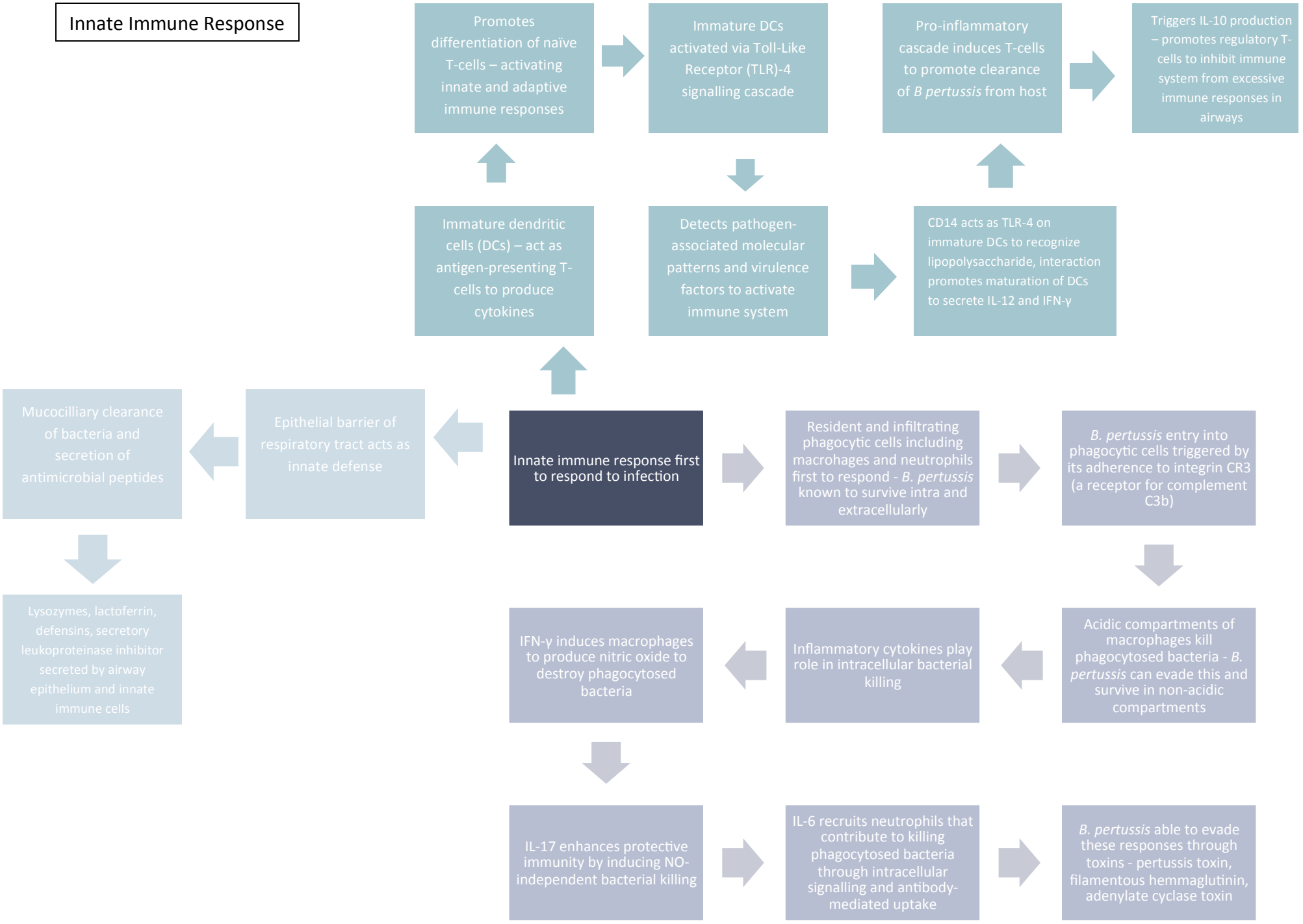
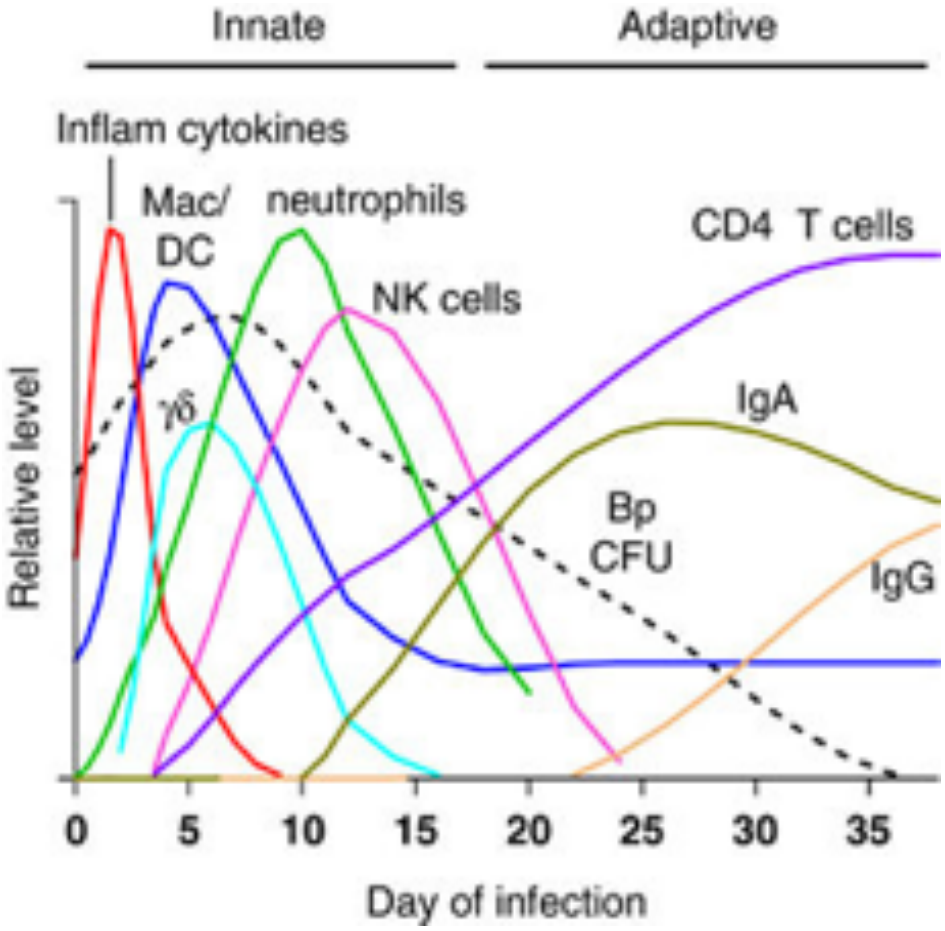
Case 4 Immune Response Summary

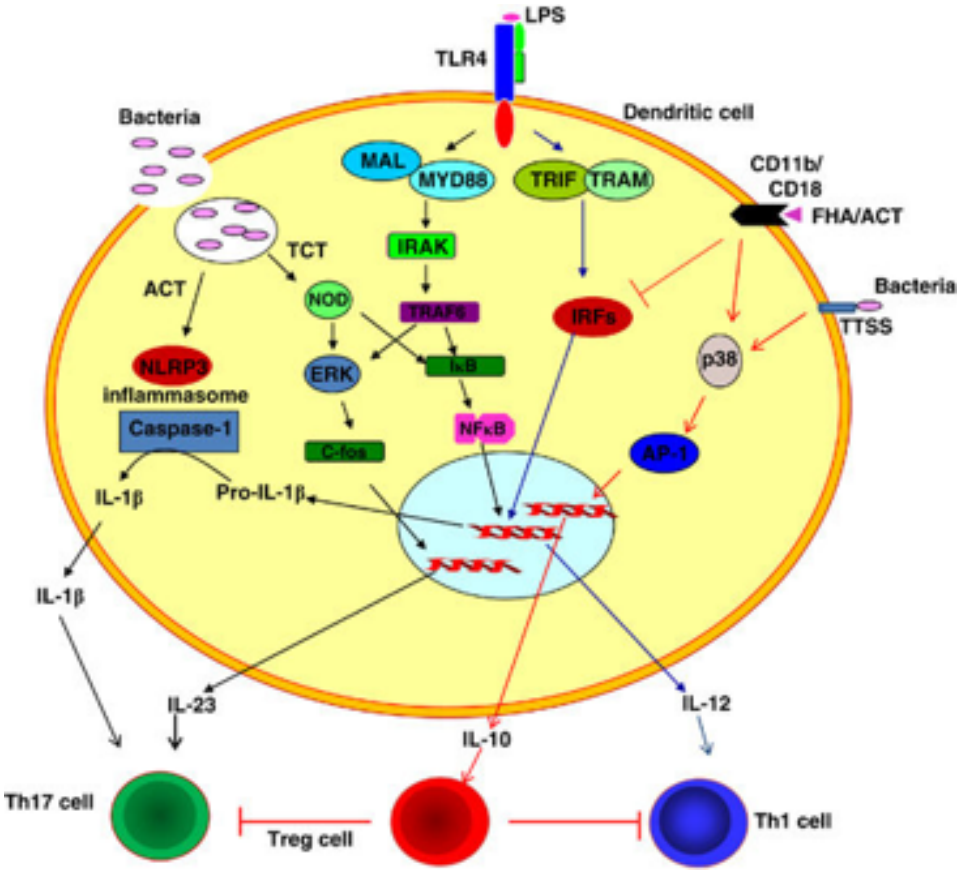
Danielle Sidsworth

Innate Immune Response



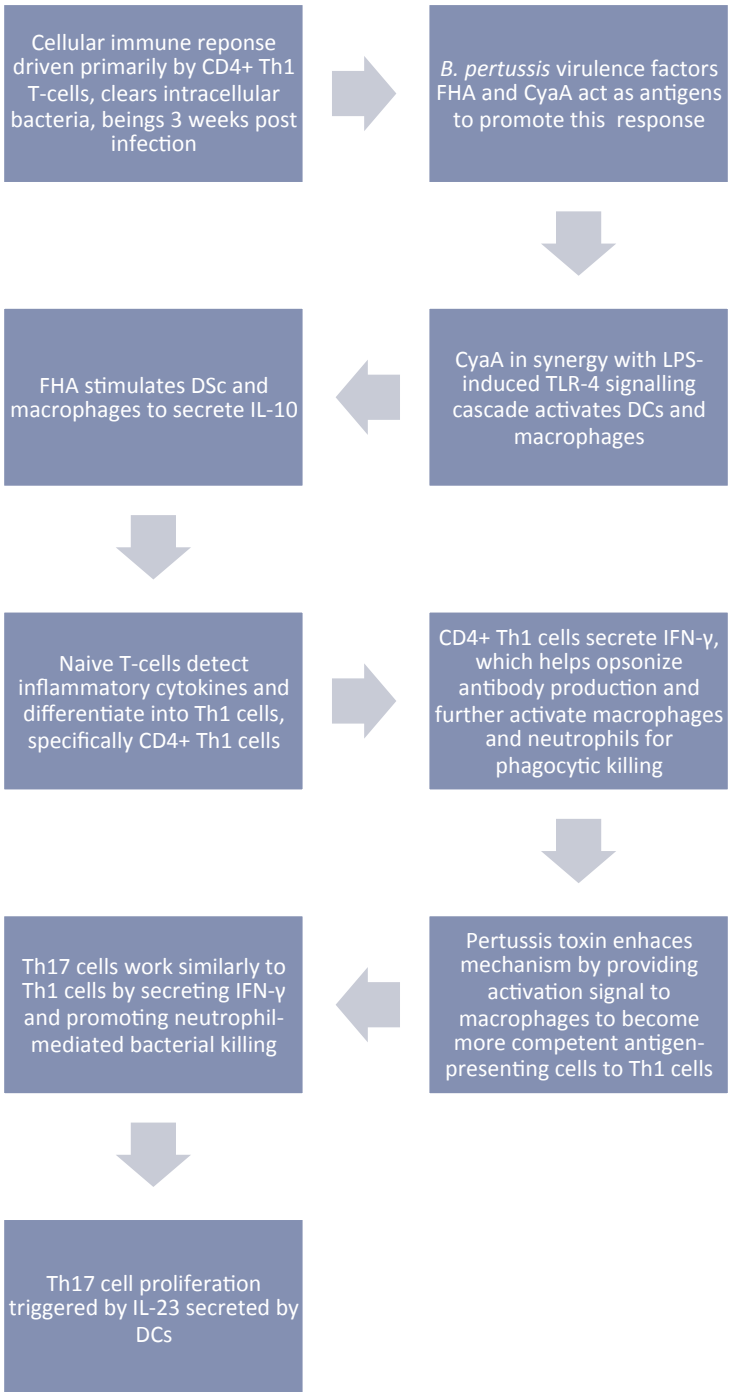


Timeline of immune response:
Innate responds first, Adaptive takes as long as 3 weeks to begin and peaks at 8 to 10 weeks



Activation of dendritic cells

Cellular Immune Response



Humoral Immune Response

Damage to host cells from immune response

Inflammatory response driven by Th1 and Th17

Damage host tissues, prevent clearing of pulmonary secretions

Activation of NFkB

Produces proinflammatory molecules such as IL-1/6/8, chemokines, Type 1 IFNs

LPS from *B. pertussis*

IL-1/6, IFN- γ, TNF released from leukocytes

Causes release of prostaglandin E2 and initiates fever in hypothalamus

Fever helps enhance host's innate immune response and stimulates leukocytes to kill pathogens

Tracheal toxin stimulates IL-1 release

Tracheal toxin inhibits ciliary beating in respiratory tract, can kill cells and damage host

Redness, heat, pain, swelling associated with inflammation may cause irritation of upper respiratory tract

Inflammation increases fluid in lungs to increase leukocyte mobility

Thick mucus and decreased ability to clear pulmonary secretions causes coughing fits

Inflammatory response causes vasodilation and increased vascular permeability – can result in edema

Signals from PAMPs release proinflammatory chemicals, activating complement system

Proinflammatory signal molecules damage neighbouring cells and cause further paralysis of cilia

Bacterial Toxin related damage

Bacterial Toxin	Description	Cellular Damage	Host Damage
Pertussis Toxin (PT)	Predominant cause for multiple physiologic, immunologic, and pharmacologic effects in the host. Made of 5 subunits: S1 subunit carries biologic activity, S2-5 subunits bind to cell membrane	**T-Cells**: proliferation, IL-2 and IFN-γsecretion, inhibit chemotaxis **NK cells**: inhibit chemotaxis **B cells**: reduce survival **Macrophages**: induce IL-1 and NO production, B7 expression, inhibit chemotaxis	Leukocytosis, splenomegaly, cell proliferation, hypoglycemia, hypoproteinemia, increased resistance to infections, increased capillary permeability
Adenylate Cyclase Toxin (CyaA)		**Macrophages**: increases intracellular cAMP to inhibit oxidative response and intracellular killing **Monocytes:** induce apoptosis **Neutrophils**: inhibit phagocytosis and phagosome-lysosome fusion	
Lipopolysaccharide (LPS)	Heat-stable endotoxin commonly produced by *Bordetella* species	**Macrophages**: induce IL-1, TNF-α, IL-6, IL-12, IL-18, and NO production	Destroys ciliated cell population in the airways
Tracheal Cytotoxin	Chemically related to peptidoglycan	**Epithelial cell:** induce IL-1 and NO production **Neutrophils:** inhibit chemotaxis and oxidative metabolism	Destroys ciliated cell population in synergy with LPS
Heat-Labile Toxin	Proteinaceous dermonecrotic toxin localized in the		Strong vasoconstrictive effects; therefore, causes tissue damage in the respiratory tract

Evading the Host Immune Response

Filamentous haemagglutinin (FHA) - critical virulence factor involved in adhesion to host cells

Promotes macrophage and neutrophil phagocytosis by binding to and activating complement receptor 3 (CR3) on target cells

This allows bacteria to avoid extracellular dection

FHA may act as suppressor of inflammation in airways, as dendritic cells exposed to FHA secrete immunosuppressive cytokines IL-10 via TLR-2 signalling pathway

Generation of IL-10 suppresses IL-12 production and promotes T cell differentiation into regulatroy T (Treg) cells

Treg cells secrete more IL-10, further suppressing IFNg production to inhibit Th1 response

FHA interferes with NFkB signalling through proteasome inhibition to suppress proinflammatory expression

Adenylate Cyclase Toxin (ACT) - enters cells by binding to CR3

Results in massive innate cellular increase in cAMP via adenylate cyclase domain

ACT facilitates formation of cation-selective pores in cell membrane through hemolysin repeat in its toxic domain, further increasing cAMP levels

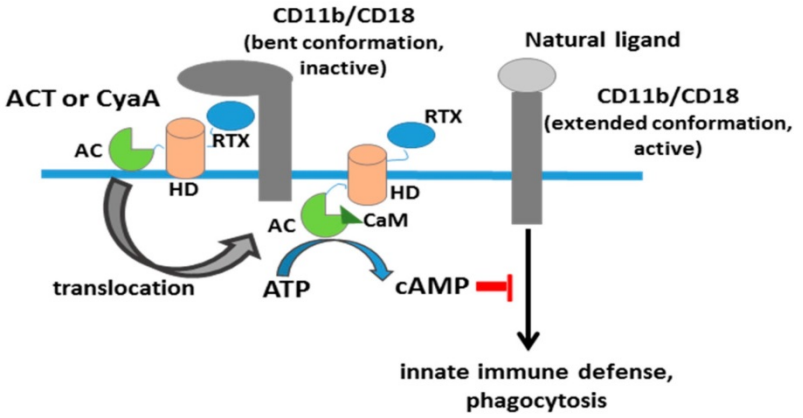
Rise in cellular cAMP results in inhibition of a variety of anti-bacterial functions

Prevents neutrophils from making extracellular traps and inhibiting their ability to undergo oxidative burst

Can induce innate immune cells to undergo apoptosis and cell cycle arrest, while hindering ability for phagocytosis, chemotaxis, and superoxide generation

Can suppress secretion of proinflammatory cytokines like IL-12 and TNF-a

Cellular cAMP increase via induction by ACT



Type Three Secretion System (TTSS)

Inhibits NFkB activation in order to block defensin expression by both airway epithelial and innate immune cells

Critical effector from TTSS, BopN, implicated in modulating immune response of effected cells

BopN contributes to upregulation of IL-10 secretion

Diminishes proinflammatory responses including inhibition o fIFNg prduction, allowing *B. pertussis* colonization easier

Pertussis toxin - made up of 2 subunits, A (S1) and B (S2-S5 oligomer)

B oligomer enhances FHA-mediated adhesion by upregulating host CR3 via receptor mimicry to facilitate bacterial uptake by innate immune cells

A subunit causes host cell to increase production of cAMP

A subunit utilizes its ADP ribosyl transferase activity to inhibit inhibitory protein Gi of adenylate cyclase

Adenylate cyclase continues to convert ATP to cAMP uncontrolled

PT mediated inactivation of Gi protein results in modulation of early immune response by inhibition of chemokine signalling pathways

Causes impaired macrophage, neutrophil, and other lymphocyte chemotaxis and infilatration to sites of infection

Results in decreased phagocytic, oxidative burst, and bactericidal properties

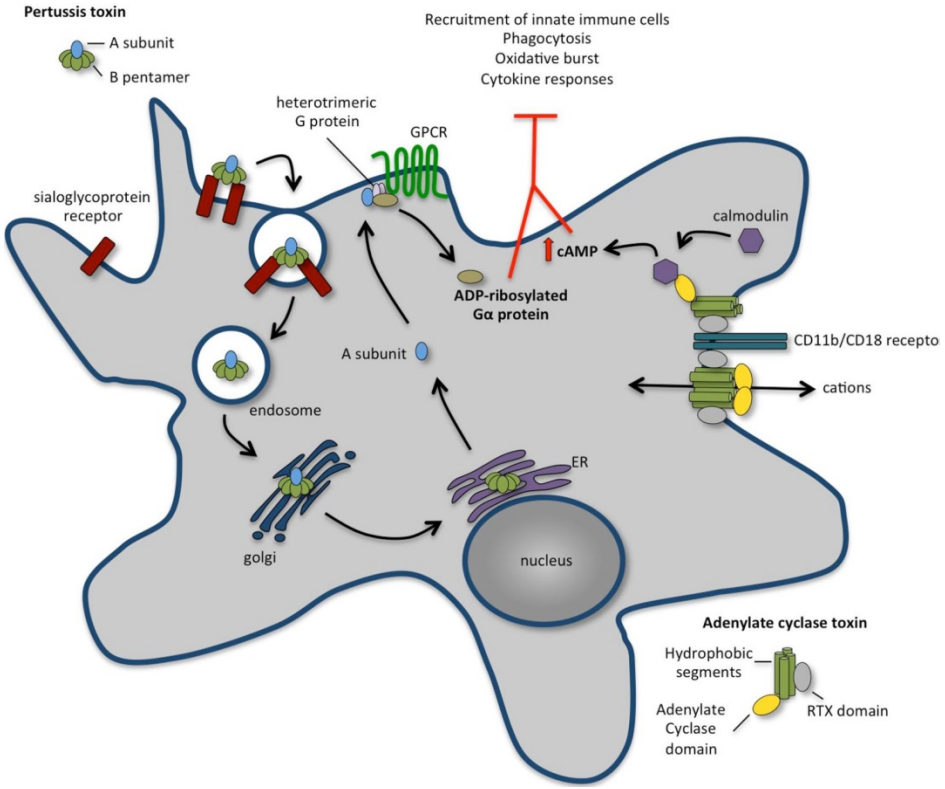
PT implicatied in delaying adaptive immune response by inhibiting phagocytosis by antigen presenting cells

This inhibition effectively limits amount of antigen processing and presentation to T cells, thus preventing adaptive response from starting

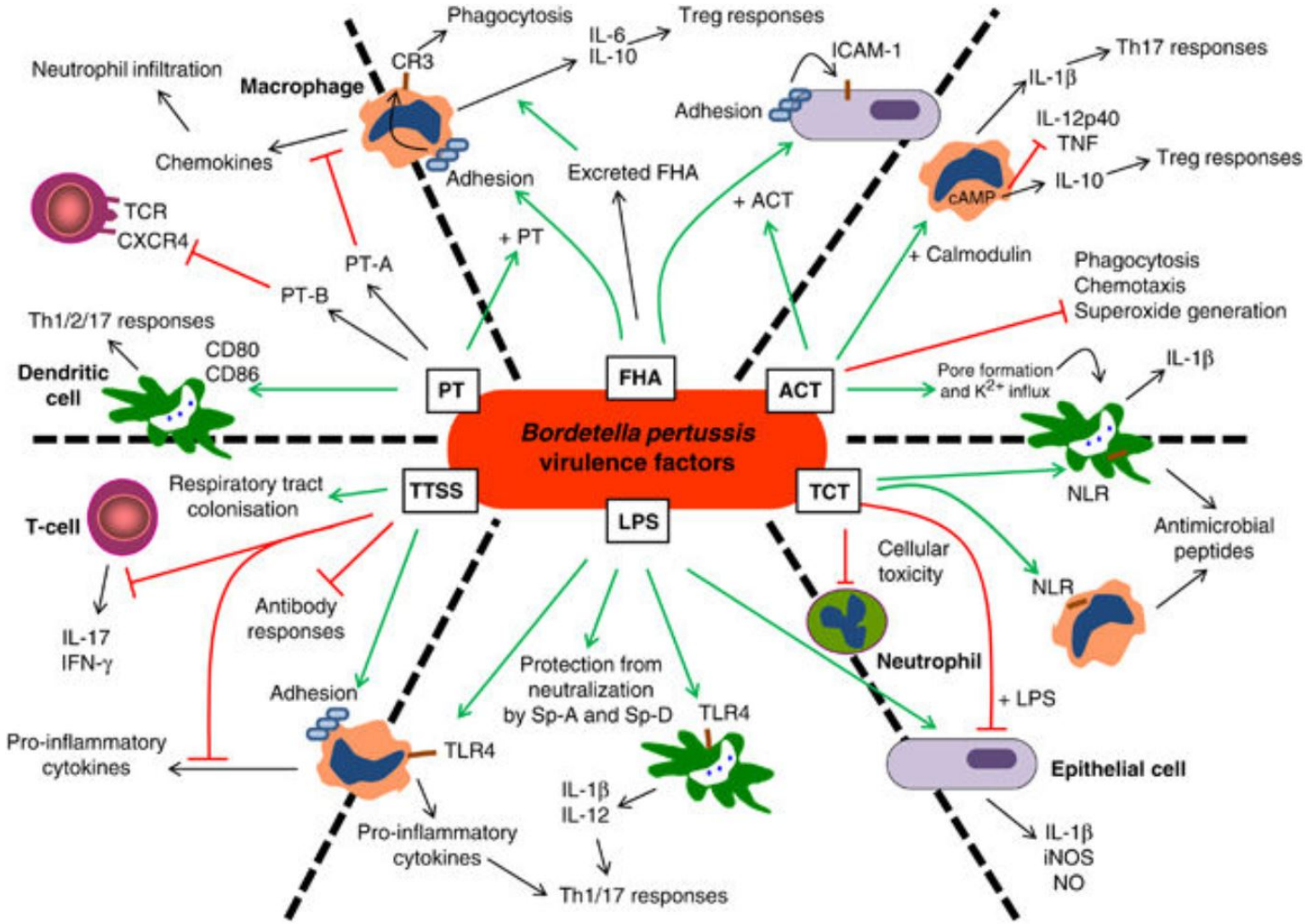
B subunit can hinder adaptive immune response in cAMP independent manner

B subunit can activate various T cell receptor signalling molecules - cause cross desensitization of TCR and chemokine receptor

Desensitization makes it harder for T cells to activatie and requires more stimulation to mediate inflammation



Pertussis toxin and evading the immune system



B. pertussis virulence factors and cellular responses

Evasion of the Complement System

Bps polysaccharide expressed on LPS surface – implicated in complement resistance

BrkA protein implicated in reducing amount of CS and C4 deposition on bacterial cell surface – decreasing frequency of MAC formation

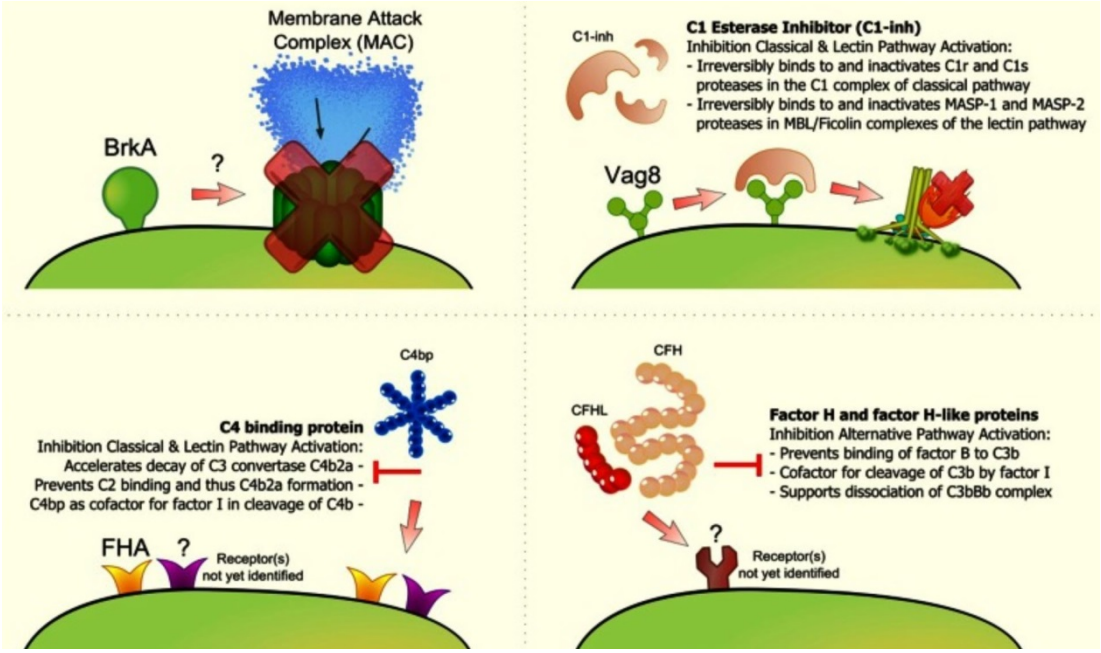
Hypothesized BrkA either inhibits C4 activation or promotes degradation of C4b on bacterial cell surface

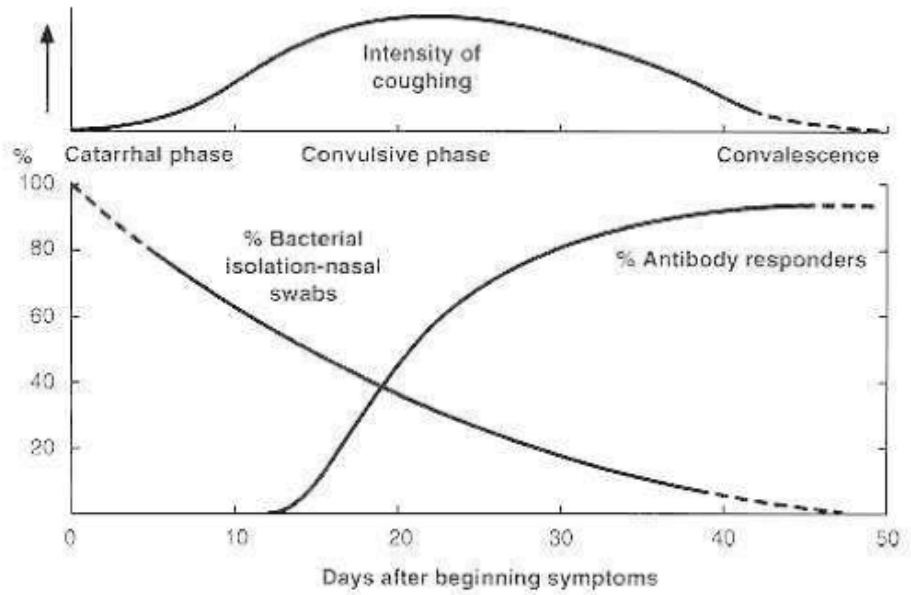
B. pertussis capable of binding C1 esterase inhibitor (C1-inh) to bacterial surface to inhibit any complement activity

C1-inh – host serine protease, regulates complement system by inactivating C1r and C1s proteases of classical and mannose-lectin pathway

B. pertussis can acquire C4b-binding protein (C4BP), a complement regulator

Uses its surface protein FHA in order to inhibit complement activation of classical and lectin pathways



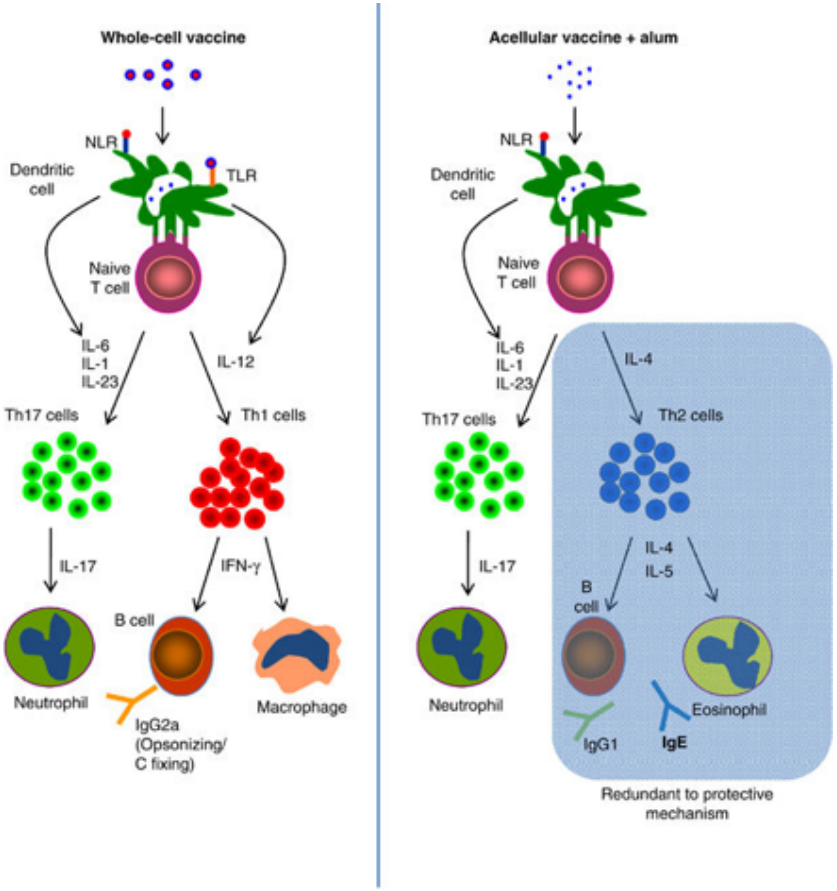


B. pertussis completely removed from body through immune responses, undetectable by 3 weeks post-infection

Following catarrhal and paroxysmal phase, which can last up to 6-10 weeks, patient recovers during convalescence phase, with paroxysmal cough less frequent.

Patient may experience symptoms for up to 2-3 months, and may experience short and long-term complications

Serum levels of *B. pertussis* neutralizing antibodies decrease rapidly after infection, however some immunity lasts 2 to 30 years following primary infection



Acellular and cellular (whole-cell) vaccines confer immunity, but no vaccine is 100% effective

Cellular vaccines induce Th1-mediated immune responses

Acellular vaccines induce Th2-mediaed responses involving antibodies

Since antibody levels often decline significantly after immunization, booster vaccines may be useful in enhancing Th2 response and IgE production for lasting immunity