Organization of the Innate Immune System: the First Line of Defense
Topics

1. Innate versus adaptive immunity
2. Components of the innate immune system
3. Pattern recognition receptors
4. Phagocytosis
5. Inflammation and recruitment
6. Bridging innate and adaptive immunity
7. Adjuvants
The New York Times Magazine

May 19, 2013

THE SECRET LIVES OF

Germs

WHAT WE CAN LEARN FROM OUR MICROBIOME. BY MICHAEL POLLAN
How does the host respond to microbes?

Host Response

MICROBES
Bacteria
Viruses
Fungi
Protozoa

NON-SPECIFIC (INNATE)
Inflammation

FIRST LINE

SECOND LINE

SPECIFIC (ADAPTIVE)
Humoral (Ab)
Cell-mediated (CMI)

No response

DEATH
Innate Immunity

1. *Adaptive immunity* requires gene rearrangements, maturation over time and highly specific antigen recognition. In contrast, *innate immunity* is:
   a. “hard wired” in germ line
   b. rapidly mobilized
   c. broadly microbicidal

2. Elements of innate immunity include pre-formed molecules that require no modification:
   a. natural antibodies
   b. alternative complement pathway
   c. basal levels of pattern recognition molecules and their receptors.
# How do innate and adaptive immunity differ?

<table>
<thead>
<tr>
<th>Innate</th>
<th>Adaptive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primitive</td>
<td>Evolutionarily recent</td>
</tr>
<tr>
<td>Non-specific</td>
<td>Antigen specific</td>
</tr>
<tr>
<td>Pattern recognition</td>
<td>Define epitope targets</td>
</tr>
<tr>
<td>First line of defense</td>
<td>Second line of defense</td>
</tr>
<tr>
<td>Necessary for proper function of adaptive immunity</td>
<td>Response improves upon repeated infection</td>
</tr>
</tbody>
</table>
Cells of the innate immune system

**Phagocytic cells:** monocytes/macrophages, PMNs, mast cells; immature DCs

**Non-phagocytic cells:** NK cells, mature DCs
Consequences of microbe-macrophage interactions

**Microbe**

- **lipid metabolites**
  - PAF
  - TXA$_2$
  - PGE$_2$

- **reduced oxygen species**
  - superoxide anion
  - OH radical
  - nitric oxide

**Cytokines**
- TNF-α, IL-1β, IL-6, IL-12, IL-15, IL-18, IFN-α/β, CSFs, chemokines, IL-10, TGF-β

**Consequences**

- **Balanced**
  - Physiological host immunity adjuvant effect

- **Dysregulated**
  - Pathological circulatory collapse
  - multiple organ failure
  - shock/death
Happy Alveolar Macrophage
# The innate immune system

<table>
<thead>
<tr>
<th>“External” Defenses</th>
<th>“Internal” Defenses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical</td>
<td>Complement</td>
</tr>
<tr>
<td>Chemical</td>
<td>Pattern Recognition Rc</td>
</tr>
<tr>
<td>Microbial</td>
<td>Interferons</td>
</tr>
<tr>
<td></td>
<td>Phagocytosis</td>
</tr>
</tbody>
</table>
## External defenses

<table>
<thead>
<tr>
<th>Intrinsic epithelial barriers to infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanical</strong></td>
</tr>
<tr>
<td>Epithelial cells joined by tight junctions</td>
</tr>
<tr>
<td>Longitudinal flow of air or fluid across epithelium</td>
</tr>
<tr>
<td>Movement of mucus by cilia</td>
</tr>
<tr>
<td><strong>Chemical</strong></td>
</tr>
<tr>
<td>Fatty acids (skin)</td>
</tr>
<tr>
<td>Enzymes: lysozyme (saliva, sweat, tears), pepsin (gut)</td>
</tr>
<tr>
<td>Low pH (stomach)</td>
</tr>
<tr>
<td>Antibacterial peptides; defensins (skin, gut), cryptidins (intestine)</td>
</tr>
<tr>
<td><strong>Microbiological</strong></td>
</tr>
<tr>
<td>Normal flora compete for nutrients and attachment to epithelium and can produce antibacterial substances</td>
</tr>
</tbody>
</table>
Protein Effectors of Innate Immunity

Defensins, Cathelicidins, Bactericidal-permeability Increasing Protein (BPI)

• Short, cationic, broad-spectrum antimicrobial proteins;
• Membranolytic;
• Secreted by myeloid cells;
• Found at mucosal surfaces (skin secretion in amphibians and fish; trachea, small intestine in mammals):
Bactericidal/Permeability-Increasing Protein in the Treatment of Sepsis

- 55 kDa cationic PMN granular protein released during activation.
- Neutralizes LPS and kills GNB by N-terminal region.
- Recombinant 21 kDa N-terminal fragment mimics whole molecule.
- Effective in animal models of sepsis (LPS and bacteremia).
- Safe and active in human LPS infusion studies.
The innate immune system

**“External” Defenses**
- Mechanical
- Chemical
- Microbial

**“Internal” Defenses**
- Complement
- Pattern Recognition Rc
- Interferons
- Phagocytosis
Adaptive ImR

**CLASSICAL PATHWAY**

Antigen:antibody complexes (pathogen surfaces)

- C1q, C1r, C1s
- C4
- C2

**MB-LECTIN PATHWAY**

Mannan-binding lectin binds mannose on pathogen surfaces

- MBL, MASP-1, MASP-2
- C4
- C2

**ALTERNATIVE PATHWAY**

Pathogen surfaces

- C3
- B
- D

---

**Innate ImR**

**C3 convertase**

- C4a
- C3a, C5a

- Peptide mediators of inflammation, phagocyte recruitment

- Binds to complement receptors on phagocytes

- Opsonization of pathogens

- Removal of immune complexes

- Terminal complement components
  - C5b
  - C6
  - C7
  - C8
  - C9

- Membrane-attack complex, lysis of certain pathogens and cells

**Complement-mediated responses**
Pattern recognition receptors

1. Toll-like receptors (10 human, 12 mouse, 222 in sea urchins)
2. Nucleotide-binding oligomerization domain (NOD)-like receptors
3. RIG-I helicase receptors
4. C-type lectins
5. AIM2
6. Stimulator of Interferon Genes (STING)
7. Mannose binding lectin
8. Macrophage mannose receptor
9. Scavenger receptors
10. CD14
11. Complement receptors
The Four Major Classes of Pattern-Recognition Receptors and Their Most Important Ligands

TLRs
- Triacyl lipopeptides
- Diacyl lipopeptides
- Flagellin
  - TLR1, TLR2
  - TLR6, TLR2
  - TLR5
  - LPS
  - Mannans

CLR
- Mannans
  - Dectin-2
  - FcγR

NLRs
- Peptidoglycan
  - DNA, RNA
  - Candida
- NLRP3 inflammasome
  - LRR
  - CARD
  - Caspase-1
- NLRC4 inflammasome
  - LRR
  - NACHT
  - CARD
  - Caspase-1

RIG-1 helicases
- MDA5
  - Long dsRNA
- RIG-1
  - Short dsRNA

N Engl J Med 2011;364:60-70
Toll-like Receptors and Agonists

*Endogenous agonists

Lipoarabinomannan
Triacylated bacterial Lipopeptides (OspA, Pam3Cys)
19 kDa Mtb lipoprotein AraLAM
*HMGB1

P. gingivalis LPS
L. interrogans LPS (?2/1 or 2/6?)

Zymosan MALP2
(& other diacylated lipopeptides)
F. tularensis LVS

Enterobacterial LPS
RSV F protein
chlamydial Hsp 60
Pneumolysin
Taxol (murine)
Ft DnaK

*Hsp 60/70?
*fibrinogen
*fibronectin
*Surfactant Protein A
*mDF2b
*hyaluronic acid fragments
*HMGB1

Flagellin (not H. pylori FlaA)
UPEC profilin

TLR2/1
TLR2/6
TLR4
TLR5
TLR11 (murine)
TLR10

Extraacellular TLRs

Endosomal TLRs

dsRNA, polyI:C
ssRNA, Imiquimod
Resiquimod (mu)

Resiquimod (hu)
CpG DNA

*HMGB1
*Endogenous agonists

Extracellular TLRs

Courtesy of S.N. Vogel
NOD-Like Receptors (NLRs)
The Many Flavors of Inflammasome
STING-Associated Vasculopathy with Onset in Infancy — A New Interferonopathy

Figure 1. STING–Interferon Pathway.
Phagocytosis involves:

1. Recognition of microbial products by pattern recognition receptors.
2. Migration of phagocytes to site of infection.
3. Adhesion of microbes to phagocytes via receptor-, antibody-, or opsonin-mediated mechanisms.
Events During Phagocytosis

Opsonins

Microbe-controlled Activating Signals

Activating Signals

Fc Receptors
Complement Receptors
Scavenger Receptors
Other Integrins
Lectins

Microbe-controlled Inhibitory Signals

Inhibitory

Membrane Traffic
Cell Division
Apoptosis
Microbial Killing
Inflammatory Cytokine/Chemokine Production

PI 3-Kinase
Phospholipase C

Antigen Presentation
Migration/Motility
Phagocytic Maturation
Actin Remodelling

Microbe-controlled Inhibitory Signals

Rho GTPases
PMN Killing Mechanisms

Azurophillic (also known as primary) granules:
- BPI
- Neutrophil elastase
- Cathepsin G
- Protease 3
- Azurocidin
- Myeloperoxidase

Nets that trap bacteria and neutrophil elastase

Specific and tertiary granules:
- Lactoferrin
- Lipocalin
- Lysozyme
- LL37
- MMP8
- MMP9
- MMP25

Calprotectin

Myeloperoxidase

Phox

O₂⁻

H₂O₂

HOBr

HOI

HOCl

Chloramines

•O₂

O₃

•OH
NADPH Oxidase

Glucose-6-phosphate → 6-phosphogluconolactone

Glucose-6-phosphate dehydrogenase

NADP⁺ → NADPH⁺⁺

NADPH oxidase

H₂O + O₂ → O₂⁻

Superoxide dismutase

Electron

H₂O₂ → MPO, Cl⁻ → HOCl⁻ → Cl₂

Gene | Chromosome | Approximate Frequency (%)
--- | --- | ---
 gp91phox | Xp21.1 | 67
 p22phox | 16q24 | 5
 p47phox | 7q11.23 | 33
 p67phox | 1q25 | 5
 G6PD | Xq28 | <0.01
Chronic Granulomatous Disease
Inflammation and Recruitment

**Inflammation**

– The infiltration of innate (neutrophils, macrophages) or adaptive (T and B cells) immune cells to the site in infection or injury. This inflammation is associated with *increased vascular leak* (leading to edema).

**Recruitment**

– The migration of immune cells from the peripheral tissues towards the source of a chemoattractant molecule. These chemoattractant molecules can be host-derived (*chemokines*-> 50 family members with conserved cysteine-rich sequences) or microbial (e.g. fMLP). Chemokine signal mediated by *chemokine receptors* (7 membrane-spanning, G-protein associated proteins)
Inflammation and Recruitment

Leukocyte extravasation (diapedesis)

1. Rolling attachment of leukocytes to endothelium that is mediated by selectins (P- and E-selectin).

2. Tethering (firm) attachment of leukocytes to endothelium that is by integrins (LFA-1 and VLA-4 binding to ICAM-1 and VCAM-1).

3. Transendothelial cell migration. This requires loosening of the junctions between endothelial cells.
Diapedesis

- Rolling
- L-selectin
- Neutrophil
- Shedding of L-selectin
- Integrin E-selectin
- Adhesion
- Diapedesis
- Blood-vessel wall

- Activating substances released by bacteria and damaged tissues
- Lipopolysaccharides, interleukin-1, and tumor necrosis factor α
- Phagocytosis and destruction of C3b-coated bacteria

- C3a C5a, chemokines, histamine, prostaglandins, and leukotrienes
Immunodeficiencies Caused by Defects in Innate Immunity

1. Chronic granulomatous disease (CGD) results from a defect in NADPH oxidase production and failure of phagocytes to produce adequate levels of oxygen radicals and hydrogen peroxide upon phagocytosis of microbes.

2. Leukocyte adhesion deficiencies (LAD) are a group of disorders where interaction of leukocytes with vascular endothelium are disrupted. This affects the capacity of these cells to attach to the endothelium and migrate into the tissues.

3. Complement system abnormalities (e.g. C8 deficiency) results in increased frequency of bacterial infections due to the inability to form the membrane attack complex.
Further Examples of Deficiencies/Mutations
Human Innate Immune System

• MyD88—pyogenic infections, esp. IPD *Medicine* 2010;89:403
• IRAK4—group B strep, shigellosis,, IPD
• NEMO (STAT3)—hyper IgE syndrome, recurrent IPD
• STAT1, -invasive salmonellosis, recurrent RSV, hepatosplenic mycobacteriosis;
• IL-12B, IL-12Rβ1-mycobacteria, salmonella, Klebsiella
• TLR3, TRAF3-HSV encephalitis
• IL-12/IL-23 β chain mutation—BCGosis
• IFNγR1 deficiency—BCG and other mycobacterioses.
• Anticytokine autoantibodies- *NEJM* 2012;367:725.
• *IRF8* mutation and dendritic cell development and BCGosis *NEJM* 2011
Characteristics of Immunodeficiency Due to Defective Recognition by Pattern-Recognition Receptors (PRRs).

<table>
<thead>
<tr>
<th>PRR Defect</th>
<th>Presumed Pathogenesis</th>
<th>Infections or Conditions for Which Susceptibility Is Conferred</th>
<th>Inheritance</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TLR defect</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MyD88 deficiency or IRAK-4 deficiency</td>
<td>TLR-pathway defect (exception: TLR3 pathway)</td>
<td>Pyogenic bacteria (staphylococci, streptococci), pneumococcus, pseudomonas</td>
<td>Autosomal dominant</td>
<td>Very rare</td>
</tr>
<tr>
<td>UNC93B deficiency</td>
<td>dsRNA-recognition defect</td>
<td>Herpes simplex virus (encephalitis)</td>
<td>Autosomal recessive</td>
<td>Very rare</td>
</tr>
<tr>
<td>TLR3 deficiency</td>
<td>dsRNA-recognition defect</td>
<td>Herpes simplex virus (encephalitis)</td>
<td>Autosomal dominant</td>
<td>Very rare</td>
</tr>
<tr>
<td>TLR5 deficiency</td>
<td>Flagellin-recognition defect</td>
<td>Legionella</td>
<td>Autosomal recessive</td>
<td>Common</td>
</tr>
<tr>
<td><strong>CLR defect</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dectin-1 deficiency</td>
<td>Beta-glucan–recognition defect</td>
<td>Candida, trichophyton</td>
<td>Autosomal recessive</td>
<td>Common</td>
</tr>
<tr>
<td>CARD9 deficiency</td>
<td>Beta-glucan–recognition defect</td>
<td>Candida</td>
<td>Autosomal recessive</td>
<td>Very rare</td>
</tr>
<tr>
<td>Mannose-binding lectin deficiency</td>
<td>Complement-activation defect</td>
<td>Bacteria and fungi</td>
<td>Autosomal recessive</td>
<td>Common</td>
</tr>
<tr>
<td><strong>NLR defect</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOD2 deficiency</td>
<td>Peptidoglycan-recognition defect</td>
<td>Local defense defect in Crohn's disease</td>
<td>Autosomal recessive</td>
<td>Rare</td>
</tr>
<tr>
<td>NLRP3 deficiency</td>
<td>Dysregulation of interleukin-1β</td>
<td>Autoinflammatory syndromes</td>
<td>Autosomal dominant</td>
<td>Very rare</td>
</tr>
</tbody>
</table>

* CARD9 denotes caspase recruitment domain-containing protein 9, CLR C-type lectin receptor, ds double-stranded, IRAK-4 a serine–threonine kinase, MyD88 myeloid differentiation factor 88, NLR nucleotide-binding oligomerization domain (NOD) leucine-rich-repeat–containing receptors, NLRP NOD leucine-rich-repeat pyrin domain–containing protein, NOD2 NOD-containing receptor 2, TLR toll-like receptor, and UNC93B a protein in the TLR3 pathway.
## Inflammasome-related Syndromes

### Table 1. Hereditary autoinflammatory syndromes in brief

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Abbreviation</th>
<th>Distinguishing Clinical Findings</th>
<th>Inheritance Pattern</th>
<th>Gene</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryopyrin-associated periodic syndrome</td>
<td>CAPS</td>
<td></td>
<td>Autosomal dominant</td>
<td>CIASI</td>
<td>Cryopyrin (NALP3, PYPAF1)</td>
</tr>
<tr>
<td>Familial cold autoinflammatory syndrome</td>
<td>FCAS</td>
<td>Provoked by cold exposure, brief episodes (hours)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muckle-Wells syndrome</td>
<td>MWS</td>
<td>Hearing loss, amyloidosis common</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal onset multisystemic inflammatory disease</td>
<td>NOMID/CINCA</td>
<td>Almost continuous, chronic aseptic meningitis, hearing loss, arthropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial Mediterranean fever</td>
<td>FMF</td>
<td>Episodes 1–3 days, polyserositis, amyloidosis common</td>
<td>Autosomal recessive</td>
<td>MEFV</td>
<td>Pyrin (Marenostri)</td>
</tr>
<tr>
<td>Syndrome of pyogenic arthritis, pyoderma gangrenosum, acne</td>
<td>PAPA</td>
<td>Pyogenic arthritis, pyoderma gangrenosum</td>
<td>Autosomal dominant</td>
<td>PSTPIP1 (CD2BP1)</td>
<td>PSTPIP1 (CD2BP1)</td>
</tr>
<tr>
<td>Blau syndrome</td>
<td>BS</td>
<td>Granulomatous inflammation</td>
<td>Autosomal dominant</td>
<td>NOD2 (CARD15)</td>
<td>NOD2/CARD15</td>
</tr>
<tr>
<td>TNF receptor-associated periodic syndrome</td>
<td>TRAPS</td>
<td>Long episodes (often &gt;1 wk), periorbital edema, migratory myalgia and rash</td>
<td>Autosomal dominant</td>
<td>TNFRSF1A</td>
<td>TNF-receptor type 1 (p55, CD120a, TNFR1)</td>
</tr>
<tr>
<td>Hyper-IgD syndrome</td>
<td>HIDS</td>
<td>Lymphadenopathy, starts in 1st year, high IgD, attack after immunization</td>
<td>Autosomal recessive</td>
<td>Mevalonate kinase (MVK)</td>
<td>Mevalonate kinase (MK)</td>
</tr>
</tbody>
</table>
Bridging innate and adaptive immunity

• Activation of immature dendritic cells by TLR agonists induces maturation and loss of phagocytic phenotype. These mature dendritic cells are highly efficient antigen presenting cells (APCs) for T cells. Cytokines and co-stimulatory molecules expressed by mature dendritic cells may control the differentiation of naïve T cells to Th1, Th2 or Th17 phenotypes.

• Thus, TLR ligands may act as adjuvants by activating these mechanisms.
Adjuvants

Adjuvant (Lat. Adjuvare, to help)—Ramon, 1926
Adjuvants can improve the immune response:

- Rapid response to pathogens (e.g. post-exposure prophylaxis)
- Vaccine response broadening (influenza, HIV, malaria)
- Dose sparing (use less antigen, increase global vaccine supply)
- Reduced number of immunizations
- New T cell vaccines (TB, viral, etc.)
- Vaccines for elderly (overcome immune senescence)
- Therapeutic vaccines (HPV, cancer, etc.)
CPG 7909 accelerates and enhances vaccine response compared to vaccine alone (saline).
Categories of Adjuvants

Antigen delivery systems:
- Alum
- Liposomes
- Virosomes
- Oil-in-water emulsions
- Microparticles
- ISCOMs
- Virus-like particles
- Carriers
- Vehicles

Immunopotentiators
- Mycobacterial, bacterial and plant derivatives
- MPL and other PAMPs (flagellin, CpG)
- Lipopeptides
- Saponins
- Small molecules (e.g. resiquimod)
- Polymers (β-glucans, inulin)
- Cytokines
Categories of Adjuvants

Antigen delivery systems:
- Alum
- Liposomes
- Virosomes
- Oil-in-water emulsions
- Microparticles
- ISCOMs
- Virus-like particles
- Carriers
- Vehicles

- “Carrier” is an immunogenic protein to which a hapten or weak immunogen is bound. Usually acts by providing T-cell epitopes to couple antigen. Are immunogenic to themselves. Can also be living organism or vector.

- “Vehicle” provides substrate for adjuvant, antigen or antigen-carrier complex. Not immunogenic.

- “Adjuvant formulation” usually adjuvant in suitable vehicle (e.g. MPL in liposome)
Mechanisms of Action

Precise mechanisms of action usually not known, but usually activates immune cells such as macrophages and DCs.…. 

• Sustained release of antigen at site of injection (depot effect);

• Upregulation of key cytokines and chemokines

• Cellular recruitment to site of infection via chemokines

• Increase antigen uptake and presentation to APC

• Activation and maturation of APC (increase MHC class II and co-stimulatory molecules), migration to draining LN

• Activation of inflammasome
Mechanisms of Action (Cont’d)

- Adjuvants can select for, or modulate, humoral vs cellular immune response by:
  - affecting antigen processing;
  - polarizing towards a predominantly Type 1 or 2 immune response;
  - preferentially stimulating Th1 (IL-2, IFN-γ, TNF-α—e.g. MPLA, MDP) or Th2 (IL-4, IL-5, IL-6, IL-10—e.g. alum, MF59) CD4+ T helper cells;
  - modulating antibody avidity, specificity, quantity, isotype, subclass
Chitosan: An Adjuvant with an Unanticipated STING

1. Chitosan activates cGAS-STING in DCs
2. Activated cGAS-STING leads to type I IFN-dependent DC activation
3. Activated DCs drive cellular immunity

Carroll EC et al Immunity 2016 44(3):597
Adjuvants used in licensed vaccines

- **Aluminum compounds**—excellent safety record. But local rxns, inability to enhance Ab response agst certain licensed vaccines; inability to elicit CMI.

- **Microfluidized Oil/water emulsion (MF59)**—squalene emulsion with Tween 80 and Span 85. MF59 microdroplets activate immune system in absence of antigen (Novartis Vaccines adjuvanted flu vaccine with MF59).

- **ASO4**—GSK; alum salt+MPL. Used in hepatitis vaccine (*FENDrix®*) and *Cervarix®* HPV antigens as VLPs.

- **Emulsion-based formulations**—one liquid as particle within second continuous liquid. Surfactants added to stabilize emulsions. Mineral oils in water-in-oil emulsions stay at injection site (Montanide®)-severe local rxns; Oil-in-Water preps have small particles of oil in aqueous continuous phase-more easily cleared.
Adjuvants, cont’d

• **MPLA** (and synthetic lipid A mimetics-aminoalkyl glucosaminide-4-PO4s); ASO2 is O/W emulsion with MPL and QS-21. Latter used in malarial vaccine trials. Other TLR agonists: polyI:polyC (TLR3); flagelliln (TLR5); immunostimulatory oligonucleotides: e.g. CpGs-(TLR9)

• **Exotoxins**—recombinant LT—potent mucosal adjuvant. Transcutaneous.

• **Saponins**—from bark of S. American tree. Works with protein and polysaccharide vaccines, and elicits both humoral and CMI.

• Carbohydrates—easily metabolized, little accumulation. Delta inulin (Advax®) in human trials with flu and hepatitis B. Not proinflammatory.
Adjuvant effects impacted by:
- nature and dose of immunogen;
- nature and dose of adjuvant;
- stability of formulation;
- immunization schedule;
- route of administration;
- species of animal;
- genetic variation within species, including immune status.

Knowledge of properties of distinct adjuvants allows for rational design of adjuvant combinations that may lead to more effective vaccines.
• Wiley SR et al. Targeting TLRs expands the antibody repertoire in response to a malaria vaccine. Sci Transl Med 2011;3:93ra69
Bibliography


• Casanova et al, Human TLRs and IL-1Rs in host defense: natural insights from evolutionary, epidemiological and clinical genetics. *Annu Rev Immunol* 2010.