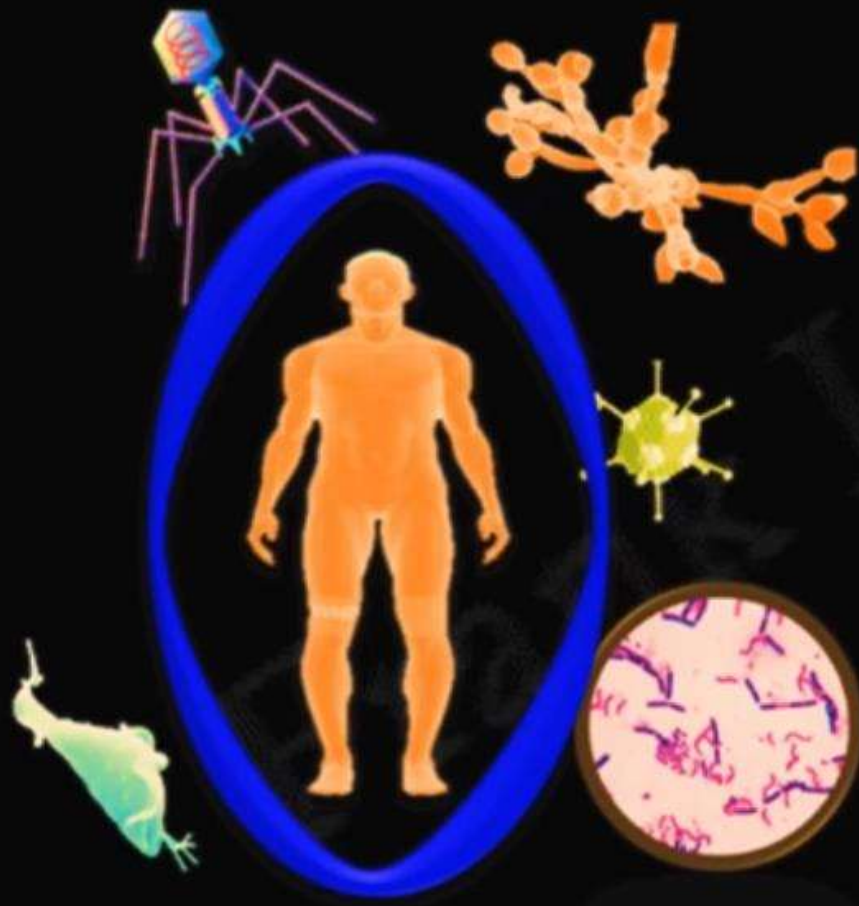


Toll Like Receptor

Slides are taken from YouTube snapshots



- Self
- Non-self

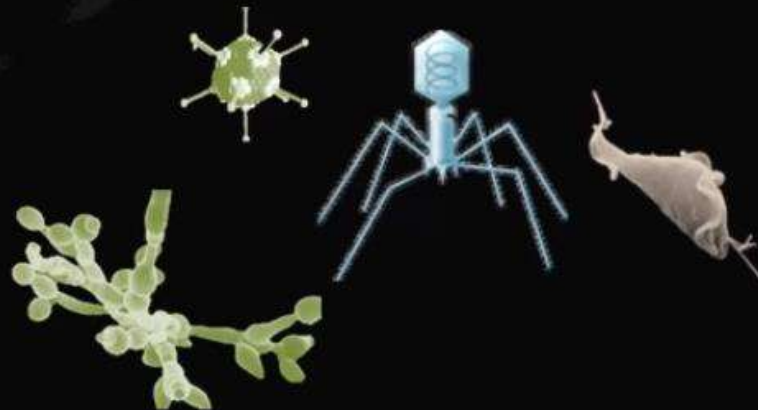
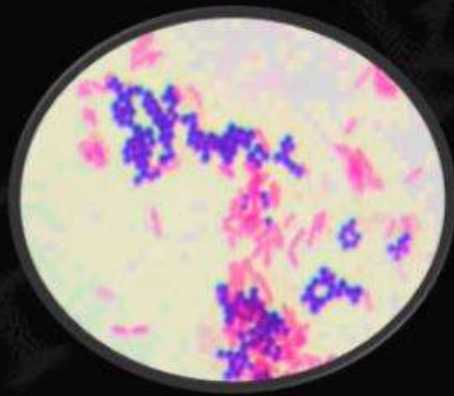


CONCEPT OF “SELF” AND “NON-SELF”

- **“Self”** refers to the cells and molecules which are part of our own body.
- **“Non-self”** (foreign) refers to cells and molecules which are not part of our body.

CONCEPT OF “SELF” AND “NON-SELF”

- “Non-self” substances are **harmful**, because they have **ability to cause damage to the body**.



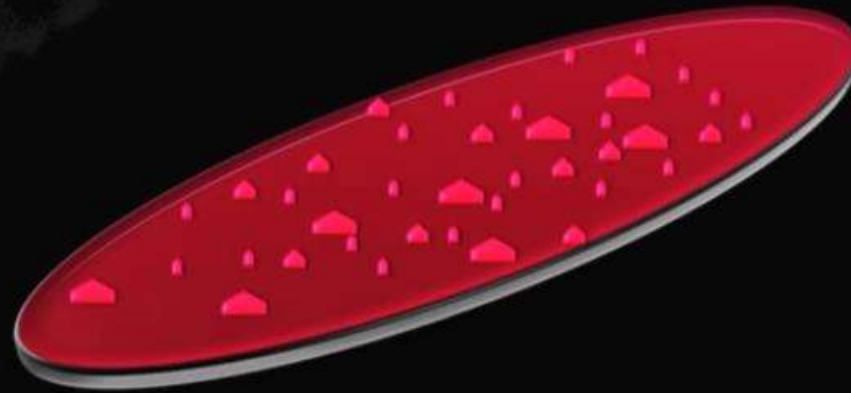


Innate Immune System



recognizes

Repeating patterns of molecular structures



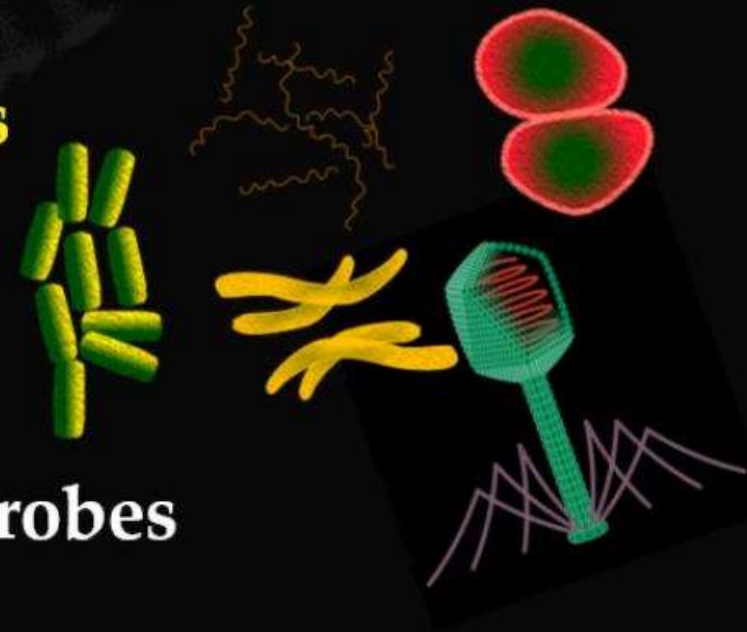
PAMPs

*P*athogen-*A*ssociated *M*olecular *P*atterns

PAMPs

Pathogen-Associated Molecular Patterns

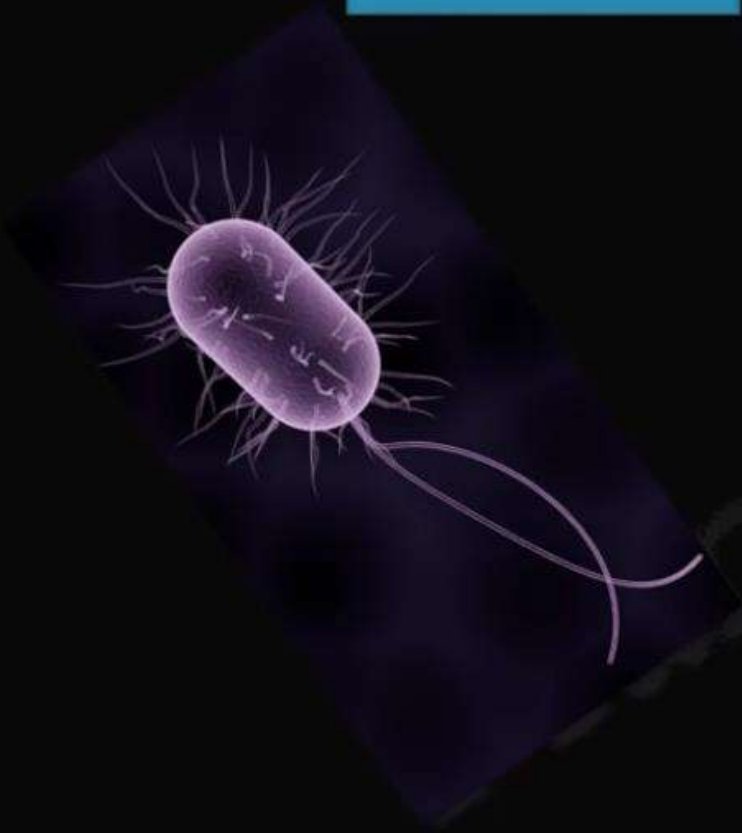
- **Unique structures** present in microbes
- **Repeating molecular patterns**
- **Absent in humans**, but present in microbes



PAMPs

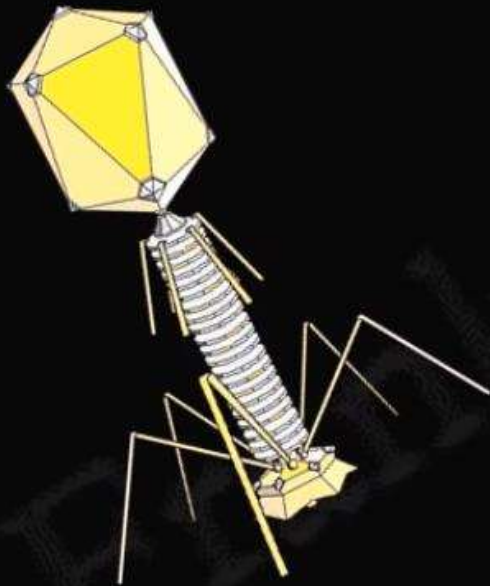
Pathogen-Associated Molecular Patterns

- **Lipopolysaccharide (LPS)** present in the outer membrane of Gram-negative bacteria
- **Lipoteichoic acid** and **peptidoglycan** in cell wall of Gram-positive bacteria
- **Flagellin** in bacterial flagella



PAMPs

Pathogen-Associated Molecular Patterns



- **dsRNA** and **ssRNA** of viruses

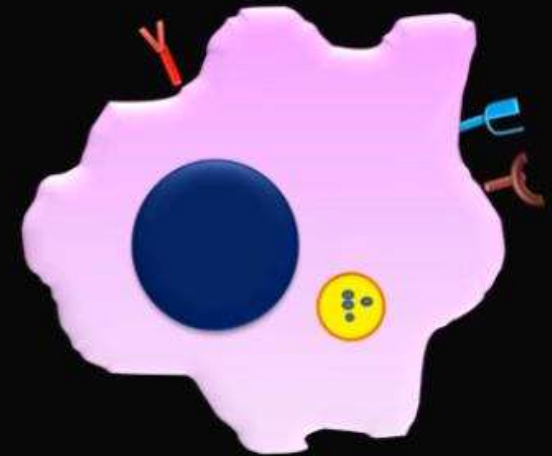
How does host's immune system
recognize these PAMPs ?



PRRs

Pattern Recognition Receptors

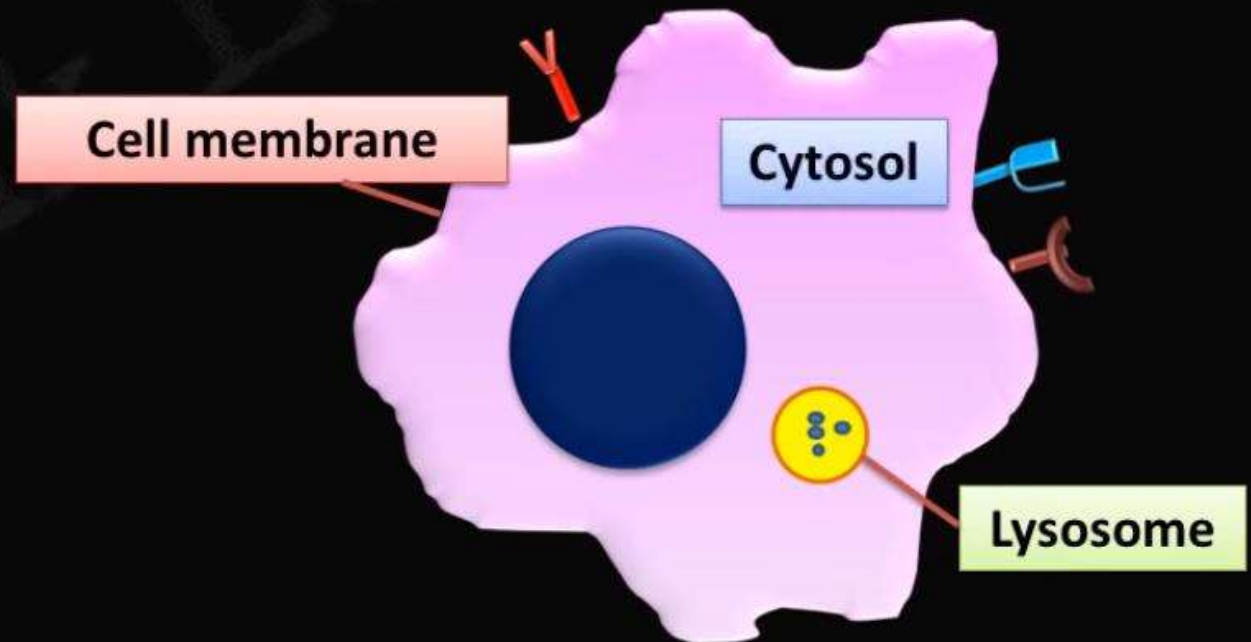
- **Receptors expressed on the plasma membrane** of cells of the innate immunity i.e on **Macrophages, Neutrophils, Dendritic Cells**



PRRs

Pattern Recognition Receptors

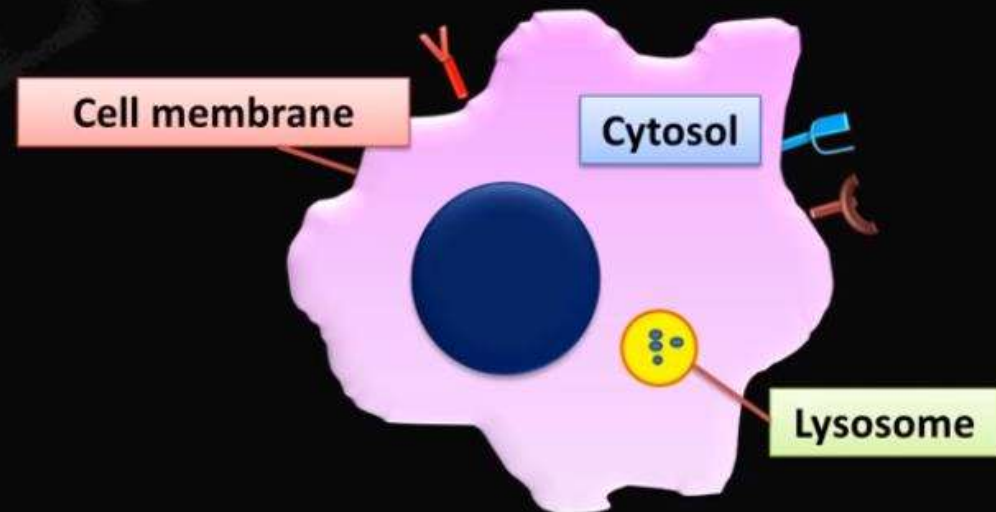
- Also present in various cellular compartments
e.g. endosomes, lysosomes and in cytosol



PRRs

Pattern Recognition Receptors

- PRRs are **able to detect extracellular as well as intracellular pathogens**



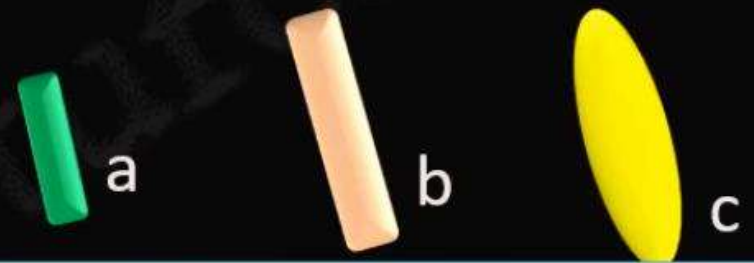
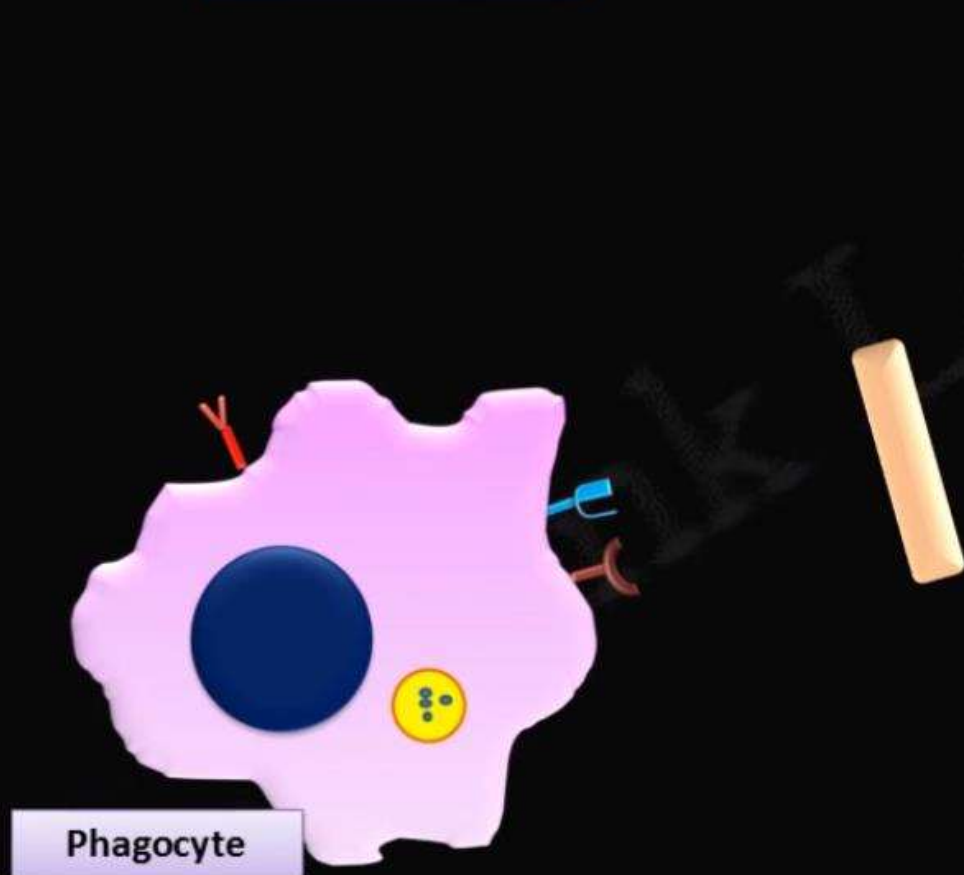
PRRs

Pattern Recognition Receptors

- Each type of PRR **can recognize multiple pathogenic species** that share a particular type of molecular pattern.

PRRs

Pattern Recognition Receptors



Different species of
Gram-negative bacteria

- *All have Lipopolysaccharide in the outer cell wall*

Types of PRRs

TLRs : Toll-Like Receptors

CLRs : C- type Lectin Receptors

RLRs: RIG-Like Receptors

NLRs: NOD – Like Receptors

TLRs : Toll-Like Receptors

- **First family of PRRs to be discovered.**
- **“Toll” is actually a gene in fruit-fly**
Drosophila melanogaster.





Figure 3-8
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W. H. Freeman and Company

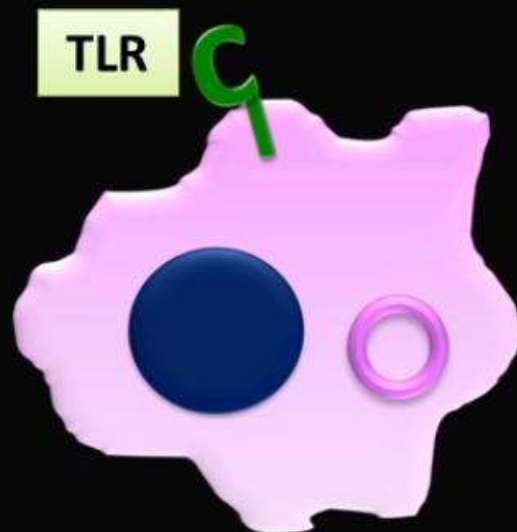
Toll-Like Receptor Signaling

- Toll receptor initially discovered in *Drosophila* as important receptor in dorso-ventral embryonic pattern
 - Toll mutants refers to the fact that these mutants could not establish a proper dorsal-ventral axis
 - Toll in German means ‘great’, apparently this was one of the words describing the scientists’ enthusiasm after observing the mutant flies
- Hoffman and colleagues showed that Toll-mutant flies susceptible to fungal infections
- Mammalian homologues discovered and designated as Toll-Like Receptors (TLR)
- TLRs recognize specific patterns in pathogens

TLRs : Toll-Like Receptors

- **Toll-like proteins have been found in animals which are known as Toll-Like Receptors(TLRs).**
- **TLRs are associated with defense against viral, bacterial and fungal infections.**

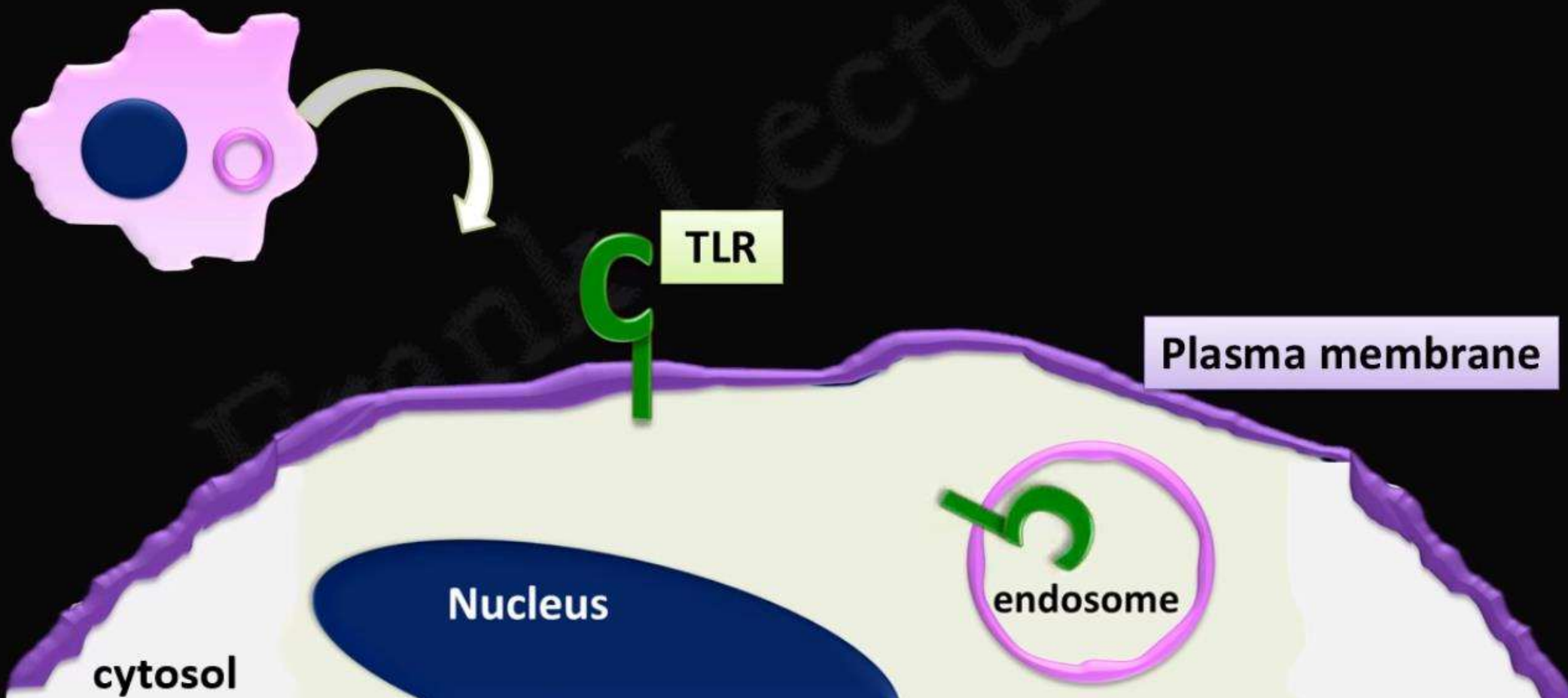
TLRs : Toll-Like Receptors



- TLRs are **membrane – spanning proteins**
- Ligand-binding pocket is **horseshoe-shaped**

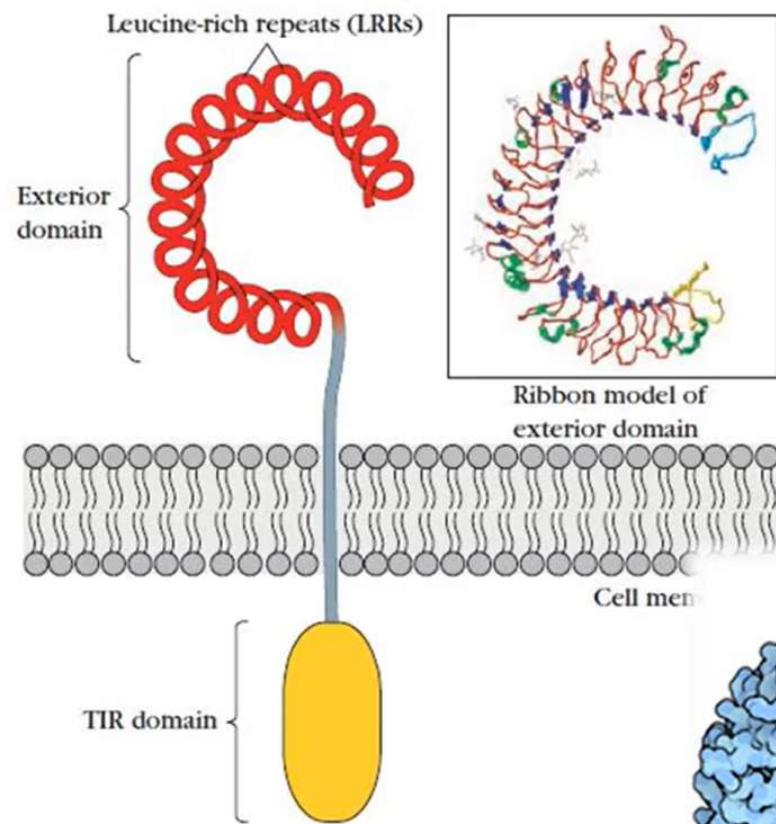


TLRs : Toll-Like Receptors



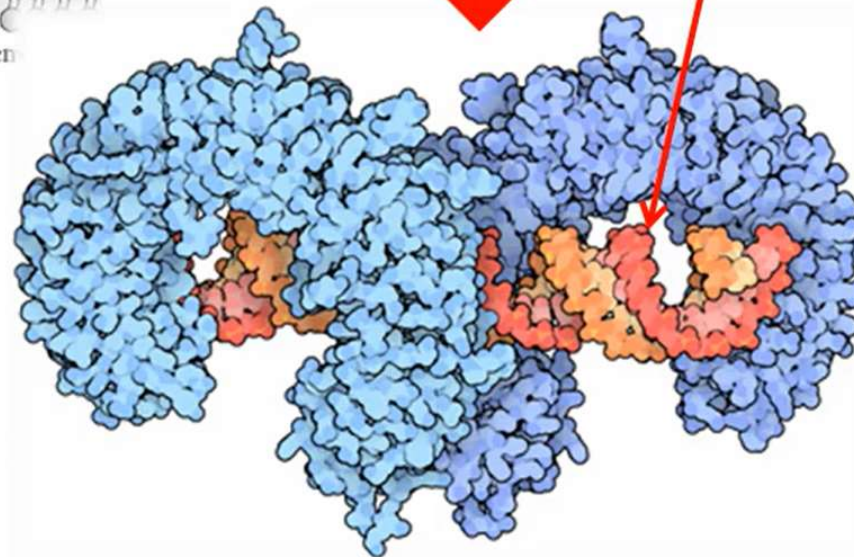
TLRs : Toll-Like Receptors

- **10 TLRs** are known for humans
- These TLRs are **specific for different components of the microbes.**



X ray Crystallographic structure

Viral dsDNA



DIMERS

HUMANS ←	TLR-1 ~ TLR-2	→	BACTERIAL TRIACYL LIPOPEPTIDES
	TLR-2 ~ TLR-2	→	BACTERIAL PEPTIDOGLYCANS, FUNGAL PHOSPHOLIPOMANNAN
	TLR-2 ~ TLR-6	→	BACTERIAL DIACYL LIPOPEPTIDES, LIPOTEICHOIC ACID, FUNGAL ZYMOJAN, GPI ANCHOR (TRYPANOSOMA CRUZI)
	TLR-2 ~ TLR-10	→	RECOGNISE LIGAND FROM LISTERIA MONOCYTOGENES
	TLR-3 ~ TLR-3	→	VIRAL dsRNA
	TLR-4 ~ TLR-4	→	BACTERIAL LIPOPOLYSACCHARIDE, FUNGAL MANNAN
	TLR-5 ~ TLR-5	→	BACTERIAL FLAGELLIN
	TLR-7 ~ TLR-7	→	VIRAL ssRNA
	TLR-8 ~ TLR-8	→	VIRAL ssRNA
MOUSE ←	TLR-9 ~ TLR-9	→	BACTERIAL CpG DNA, VIRAL CpG DNA HEMOZOIN (P. FALCIPARUM)
	TLR-11 ~ TLR-11	→	UNKNOWN
	TLR-12 ~ TLR-12	→	PROFILIN - TOXOPLASMA GONDII
	TLR-13 ~ TLR-13	→	BACTERIAL 23S RNA

TLR	LIGANDS
TLR-2	Bacterial lipoglycans, peptidoglycans
TLR-3,TLR-7, TLR-8	Viral nucleic acids
TLR-4	Bacterial LPS
TLR-5	Flagellin (bacterial flagellar protein)
TLR-9	Unmethylated CpG oligonucleotides


$$q = g = \underline{g} = C + g = C_p G \text{ DNA sections}$$