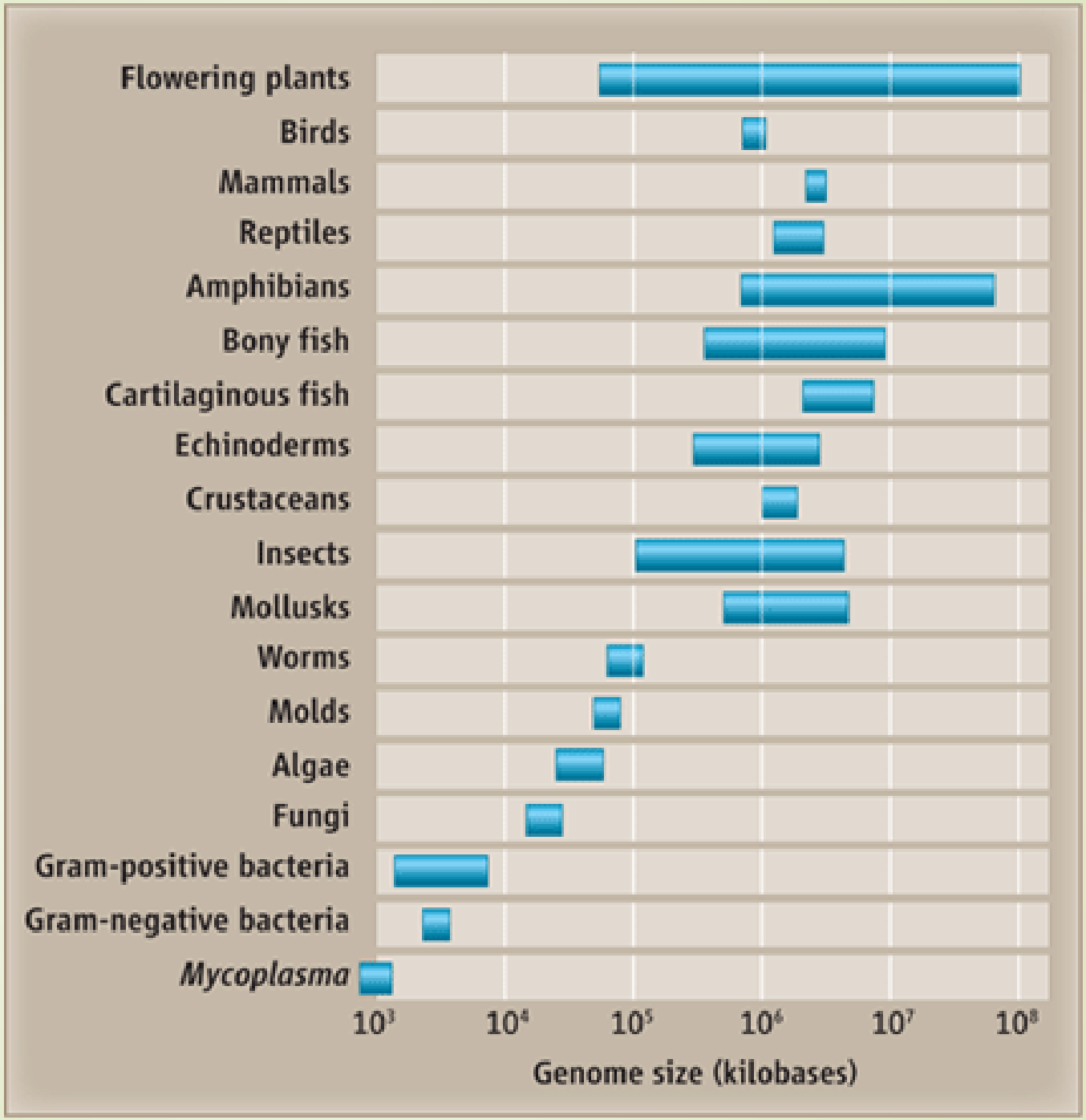
Biology of Mycoplasmas

Part 1

Biology of Mycoplasmas

- Taxonomic Class *Mollicutes*
  - No cell wall
  - Evolutionarily Gram positive
- Minimal genome
  - *M. pneumoniae* ~800 kbp / <700 ORFs
- Limited biosynthetic capacity
- Symbiotic lifestyle
  - Mammals, Birds, Fish, Arthropods, Plants


Flowering plants
Birds
Mammals
Reptiles
Amphibians
Bony fish
Cartilaginous fish
Echinoderms
Crustaceans
Insects
Mollusks
Worms
Molds
Algae
Fungi
Gram-positive bacteria
Gram-negative bacteria
Mycoplasma
10³
10⁴
10⁵
10⁶
10⁷
10⁸
Genome size (kilobases)

Mollicute strains	Host	CDS	Genome size (bp)	Accession	Citation
U. urealyticum serovar 10 str. ATCC 33699	Human	646	874478	CP001184	-
U. parvum serovar 3 str. ATCC 700970	Human	611	751719	AF222894	[45]
U. parvum serovar 3 str. ATCC 27815	Human	609	751679	CP000942	-
M. synoviae 53	Bird	659	799476	NC_007294	[46]
M. pulmonis UAB CTIP	Rodent	-	963879	AL445566	[47]
M. pneumoniae M129	Human	688	816394	U00089	[48]
M. penetrans HF-2	Human	1037	1358633	BA000026	[49]
M. mycoides subsp. mycoides SC str. PG1	Ruminant	1016	1211703	BX293980	[50]
M. mobile 163K	Fish	635	777079	AE017308	[51]
M. hyorhinis HUB-1	Swine	658	839615	NC_014448	[52]
M. hyopneumoniae J	Swine	657	897405	NC_007295	[46]
M. hyopneumoniae 7448	Swine	657	920079	NC_007332	[46]
M. hyopneumoniae 232	Swine	691	892758	NC_006360	[53]
M. genitalium G37	Human	475	580076	NC_000908	[5]
M. gallisepticum str. R(low)	Bird	763	1012800	AE015450	[54]
M. crocodyli MP145	Crocodile	689	934379	CP001991	-
M. conjunctivae HRC	Sheep and goats	696	846214	FM864216	[55]
M. capricolum subsp. ATCC 27343	Ruminant	812	1010023	CP000123	-
M. arthritidis 158L3-1	Rats and mice	631	820453	NC_011025	[56]
M. agalactiae PG2	Sheep and goats	759	877438	CU179680	-

doi:10.1371/journal.pone.0035698.t001

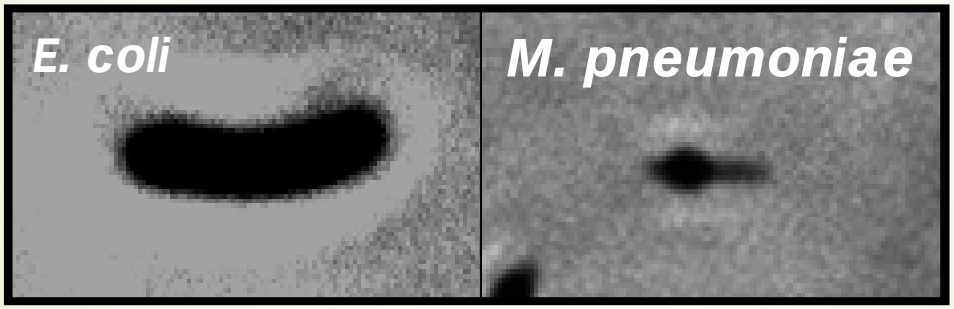
Liu W, Fang L, Li M, Li S, Guo S, et al. (2012) Comparative Genomics of Mycoplasma: Analysis of Conserved Essential Genes and Diversity of the Pan-Genome. PLOS ONE 7(4): e35698. doi:10.1371/journal.pone.0035698
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0035698

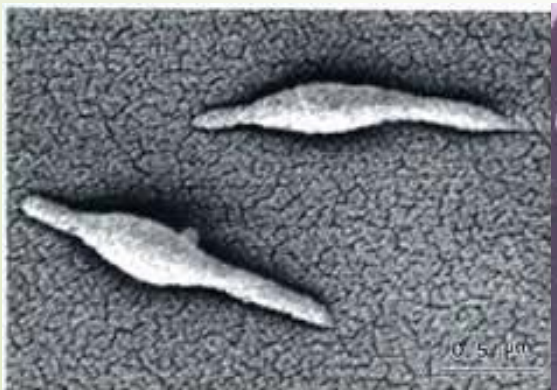
Metabolic Limitations

- No TCA cycle
- No respiratory electron transport chain
- Unable to make de novo
  - Amino acids
  - Fatty acids
  - Cholesterol
  - Purines
  - Pyrimidines

Mycoplasma cells are small and pleomorphic

- About 10% by volume the size of *E. coli*
- High surface:volume ratio





Mycoplasma Pathogens

Host	Mycoplasma	Primary Diseases
Bovine	*M. mycoides* subsp. *mycoides* SC	pleuropneumonia
	M. bovis	mastitis, pneumonia, abortion
	M. canadense; M. californicum	mastitis
	M. dispar	pneumonia
	Ureaplasma diversum	sterility, abortion
Sheep / goat	*M. capricolum* subsp. *capripneumoniae*	pleuropneumonia
	M. capricolum subsp. *capricolum*	mastitis, arthritis
	M. mycoides subsp. *capri*	pneumonia, mastitis, arthritis
	M. mycoides subsp. *mycoides* LC	pneumonia, mastitis arthritis
	M. agalactiae	infectious agalactia
	M. ovipneumoniae	pneumonia
	M. conjunctivae	keratoconjunctivitis
Swine	*M. hyopneumoniae*	pneumonia
	M. hyorhinis	pneumonia, arthritis
	M. hyosynoviae	arthritis
Poultry	*M. gallisepticum*	air sacculitis, sinusitis
	M. synoviae	air sacculitis, arthritis
	M. meleagridis	air sacculitis, sinusitis, arthritis
Dog / cat	*M. cynos*	pneumonia
	M. felis	conjunctivitis, pneumonia
	M. haemofelis ; *M. haemocanis*	anemia
Rodent	*M. arthritidis*	arthritis
	M. pulmonis	respiratory / urogenital infections
Wildlife:		
Finch	*M. galliespticum*	conjunctivitis
Tortoise	*M. agassizii*	upper respiratory tract, conjunctivitis
Alligator	*M. alligatoris*	fibronecrotic pneumonia
Human	*M. pneumoniae*	bronchitis and pneumonia
	M. genitalium	urogenital disease
	M. hominis	urogenital disease
	Ureaplasma spp.	Urogenital / neonatal disease, pregnancy
	M. fermentans	AIDS-associated disseminated infections

Acute Mycoplasma Infections

- *Mycoplasma alligatoris*
- Lethal invasive disease in caimans and alligators
- Symptoms within 1 week
- Systemic infection: necrotizing pneumonia, pericarditis, nephritis, hepatitis, meningitis
- Death within 2 weeks

M. alligatoris Disease

- Severity and dissemination suggest spreading factor
- Genomic analysis reveals hyaluronidase and sialidase
  - Hyaluronic acid is high MW polysaccharide consisting of repeating disaccharide
    - Amino sugar + uronic acid
    - Common in connective, epithelial, and neural tissue as component of extracellular matrix
    - Hyaluronidase decreases viscosity of connective tissue, facilitating spread of infection
    - Releases N-acetylglucosamine as nutrient source
  - Sialic acids protect against hydrolysis of polysaccharides, glycoproteins, and glycolipids
    - Sialidase could promote both spread and growth

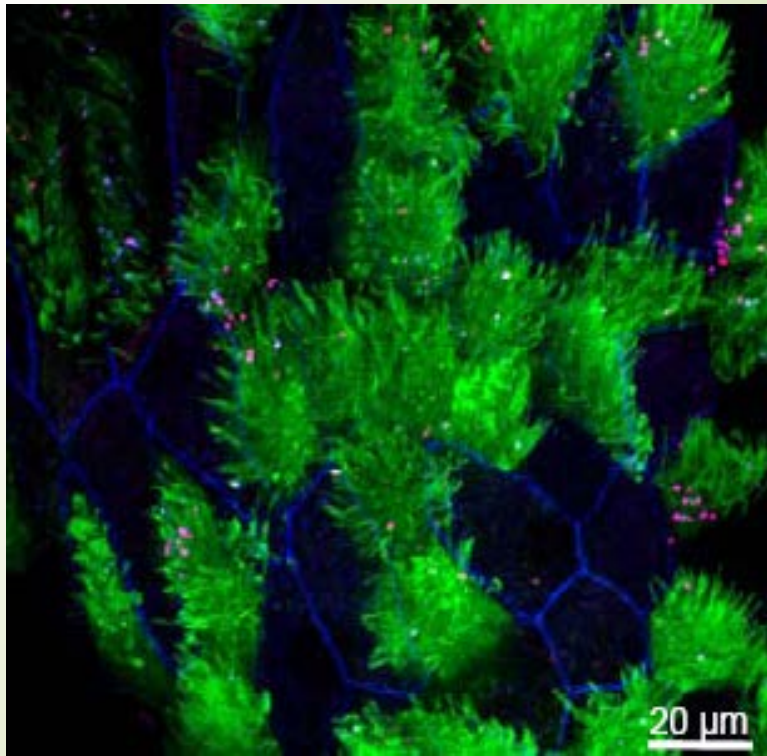
M. alligatoris Evolution

- Mycoplasmas are thought to be descendants of clostridial ancestors
- *M. alligatoris* hyaluronidase gene has high homology to that in some clostridial species
- Yet hyaluronidase is unique to *M. alligatoris* and *M. crocodyli*
- **Explanations?**

Chronic Mycoplasma Infections

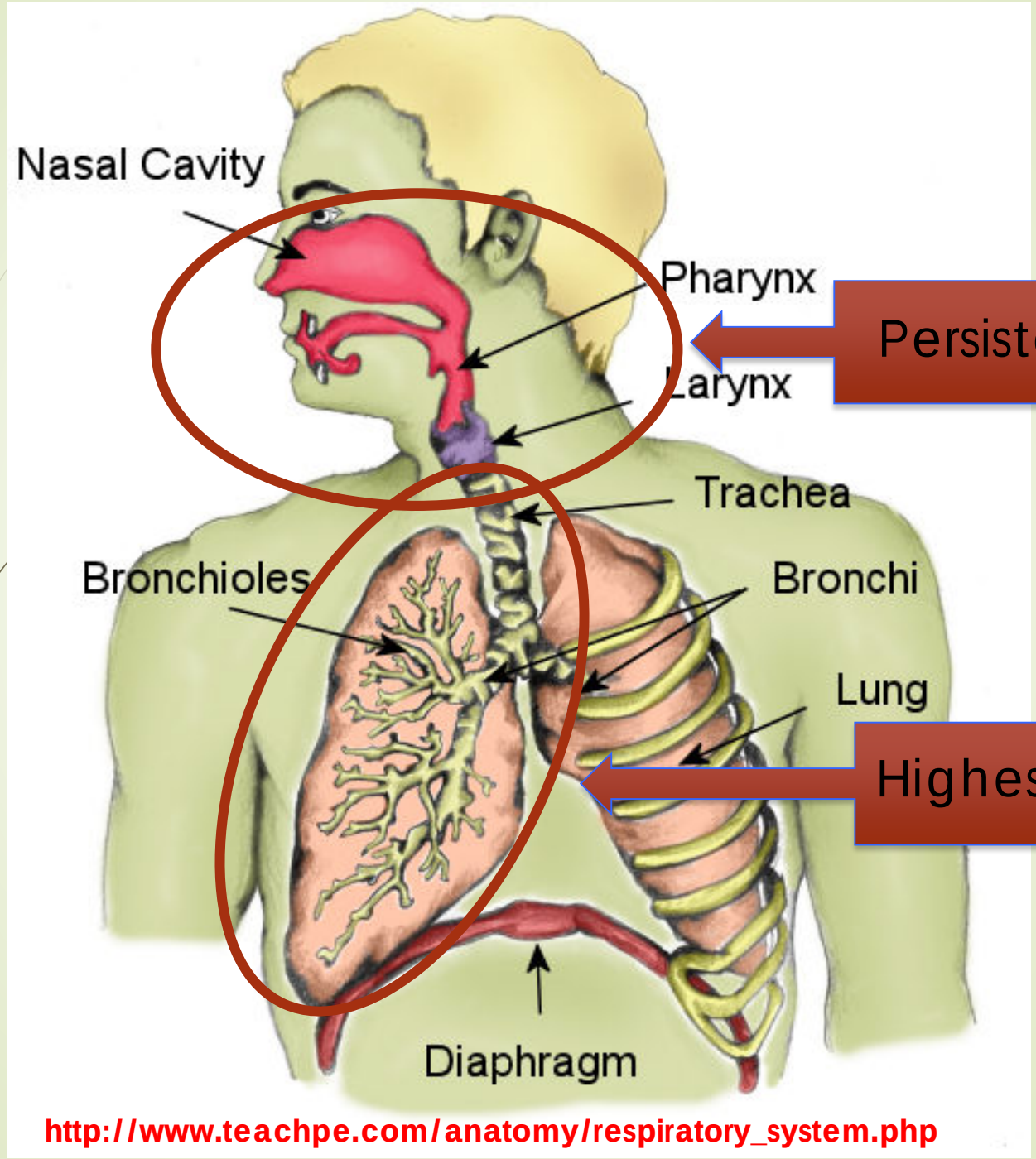
M. pneumoniae Disease: Classical Spectrum

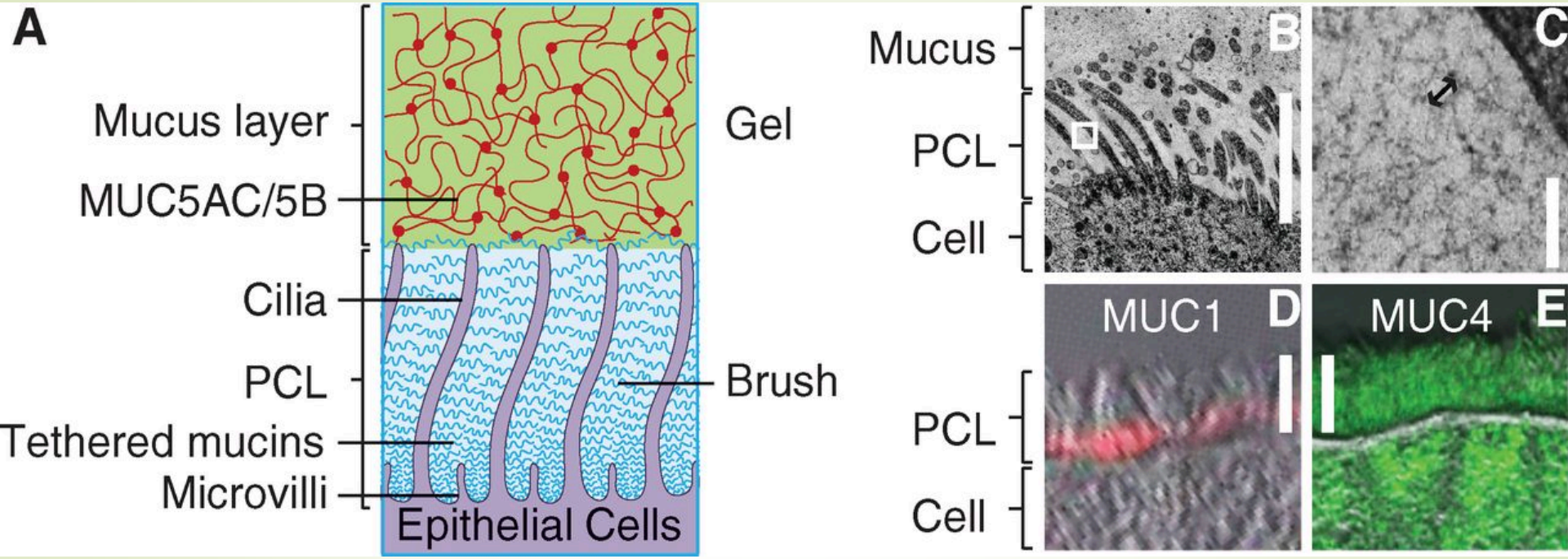
- Infections of the conducting airways
  - Especially in older children & young adults
  - Bronchitis & pneumonia
- "Walking pneumonia"
- Flu-like symptoms
- Non-productive cough
- Chronic nature = Persistence
- Carriers

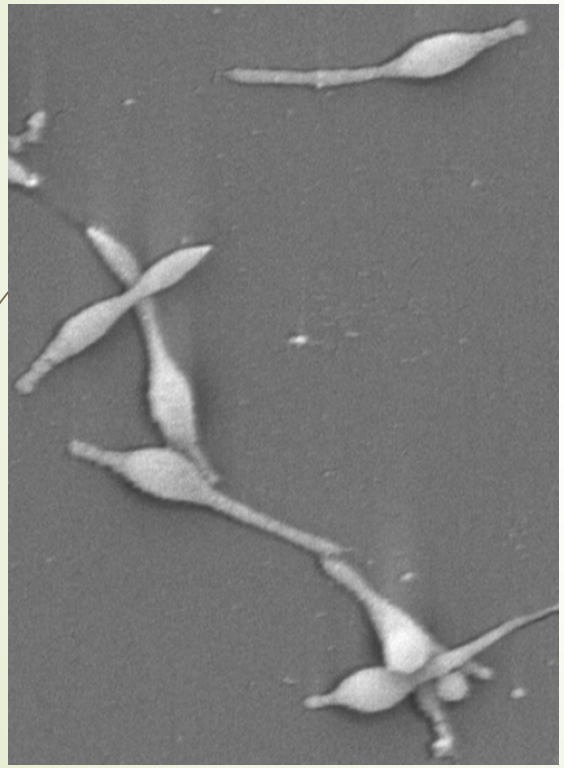


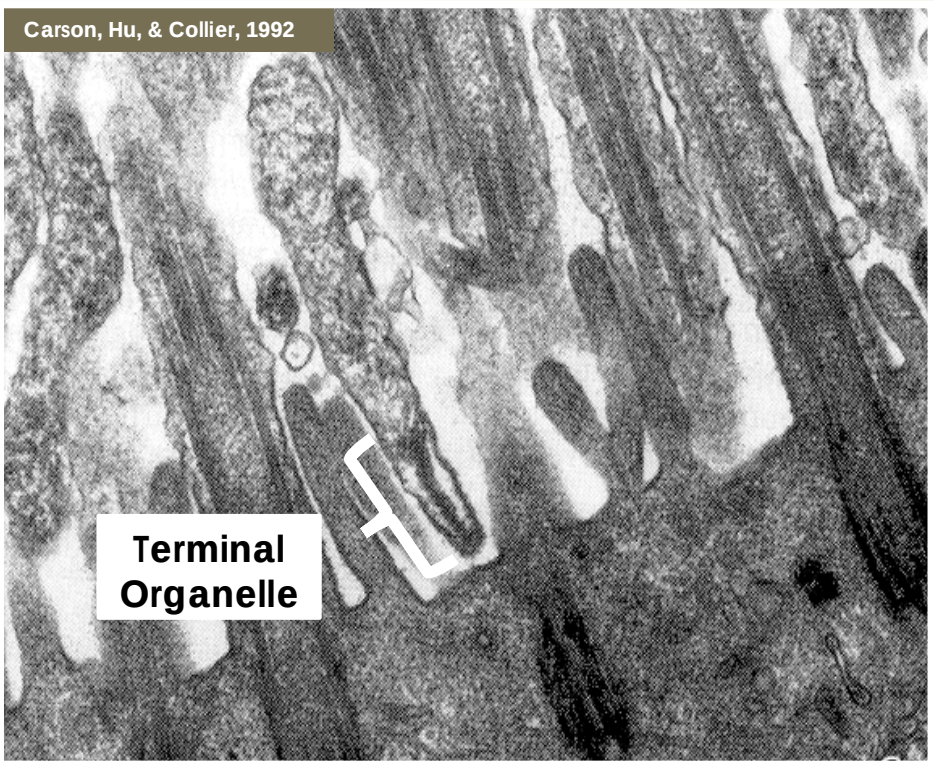
M. pneumoniae Disease: Expanding Spectrum

- Higher incidence in preschoolers & elderly
  - Better detection / more out-of-home care
  - Underscores community-acquired nature
- "Walking pneumonia" ≠ benign infection
  - Chronic / permanent lung damage
  - Clear association with asthma
  - Extra-pulmonary symptoms (15-20%)
  - Life-threatening vs life-changing
- Antibiotic treatment failures

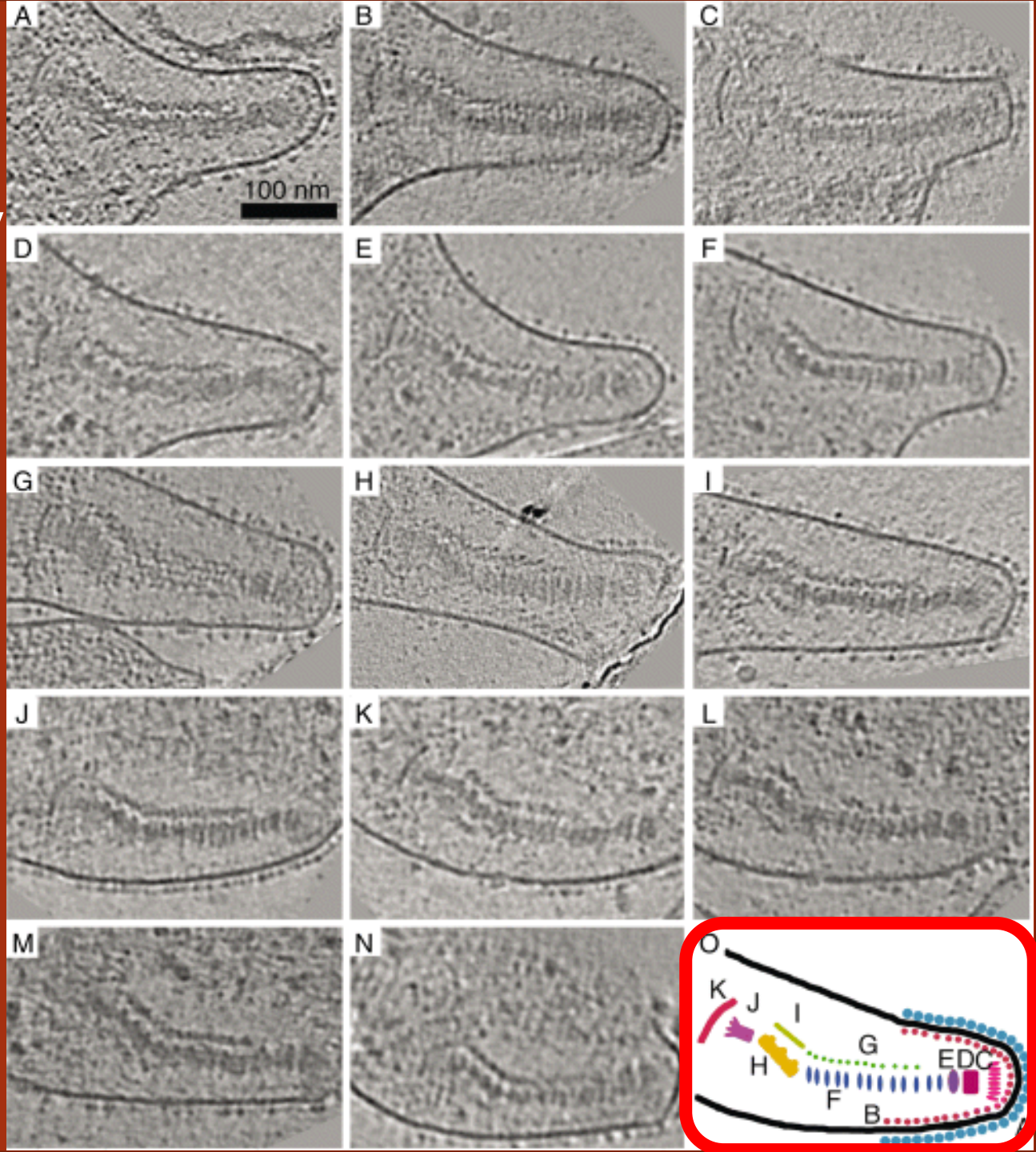

Nasal Cavity
Pharynx
Larynx
Trachea
Bronchioles
Bronchi
Lung
Diaphragm
Persistence
Highest titers
http://www.teachpe.com/anatomy/respiratory_system.php


A
Mucus layer
MUC5AC/5B
Cilia
PCL
Tethered mucins
Microvilli
Gel
Brush
Epithelial Cells
Mucus
PCL
Cell
B
C
MUC1
D
MUC4
E
PCL
Cell



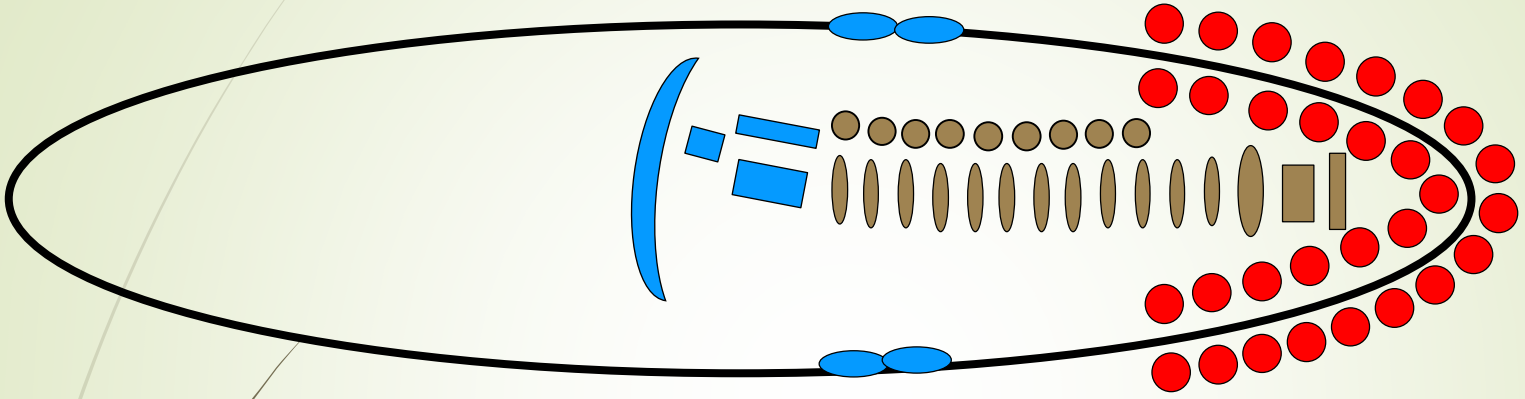

Carson, Hu, & Collier, 1992
Terminal Organelle

Electron cryotomography reveals complex substructures



Henderson and Jensen, 2006

P41, P24, HMW1, TopJ HMW2, HMW3 P1, P30, P65, B, C



Correlating Terminal Organelle Substructures and Component Proteins

M. pneumoniae Virulence Factors

- Adherence
- Gliding Motility
- CARDS Toxin
  - Community-Acquired Respiratory Distress Syndrome Toxin
  - ADP-ribosylation
  - Vacuolation
  - Inflammasome activation
  - Robust inflammation and cytopathology
- H_2O_2 Production
- Immunopathology

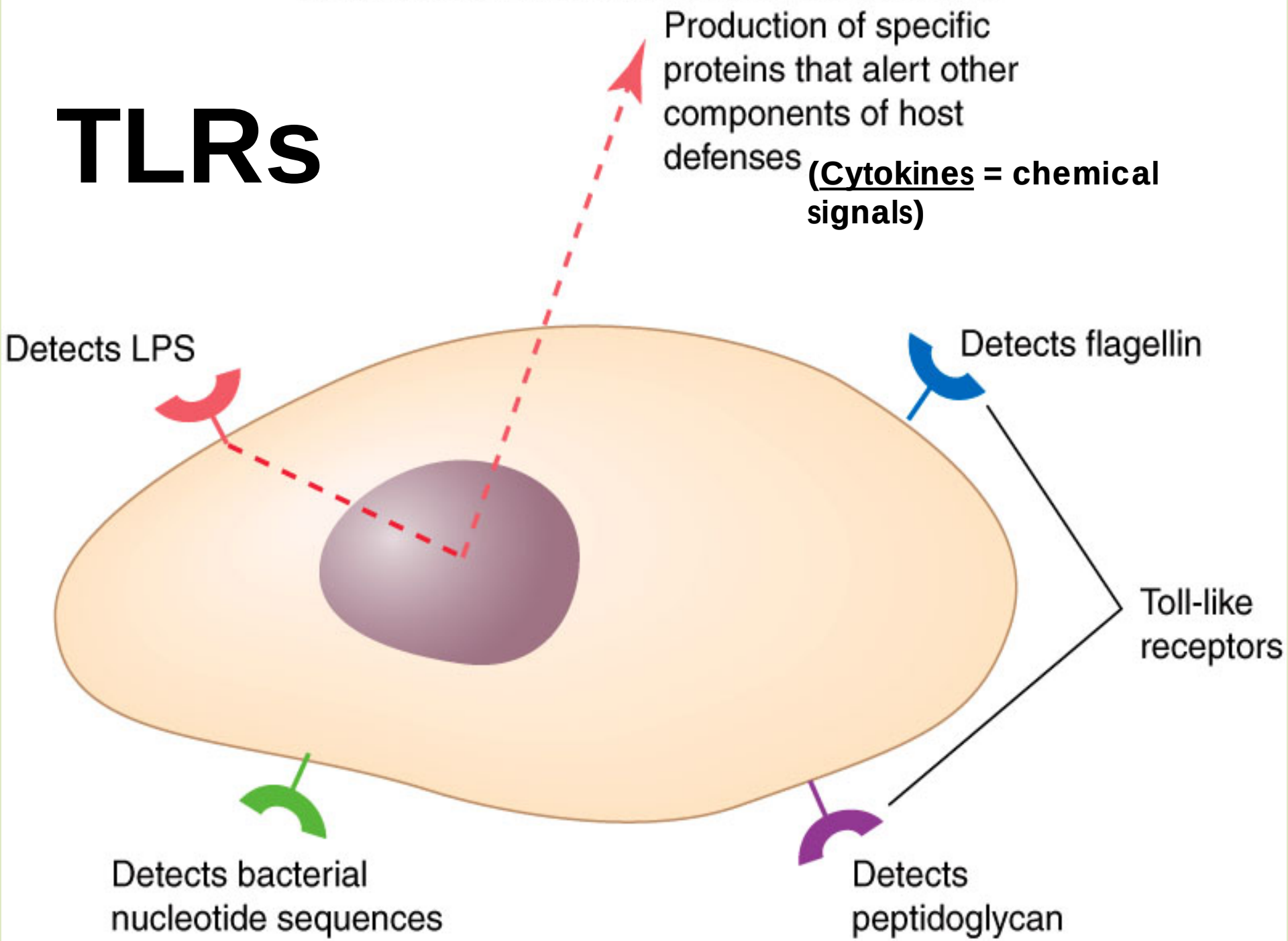
Immune Defenses

- Physical Barriers
  - Mucociliary escalator
- Innate Defenses
  - What is inflammation?
  - Toll-like Receptors and Pro-inflammatory Cytokines
- Adaptive Defenses
  - Antibodies to block colonization

Toll-Like Receptors (TLR)

- Pathogen Molecular Pattern (PAMP) Recognition
  - **Alarm activated by intruders**
  - Allow cells to detect molecules associated with microbes
  - NOD proteins do same for inside cell – virus detection
- 2011 Nobel Prize

TLRs



TLR and Pro-inflammatory Cytokines

- Mycoplasma lipoproteins activate TLR1, TLR2, and TLR6
- Trigger production of pro-inflammatory cytokines
- Cell signaling molecules that promote upregulation of inflammatory reactions
- Work with cells such as neutrophils and macrophages
- Include:
  - IL-1β
  - IL-6
  - TNFα