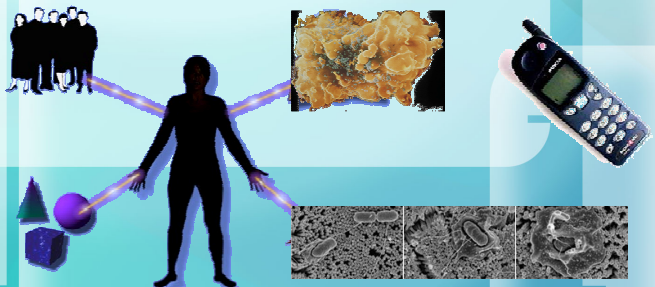
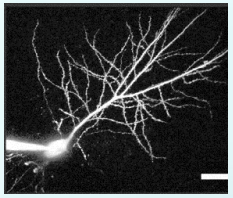
Communication In Infection



NUVEE PRAPASARAKUL
Department of Vet Microbiology,
Faculty of Veterinary Science, Chulalongkorn University

BIOCOMPLEXITY

Extracellular Signaling molecule

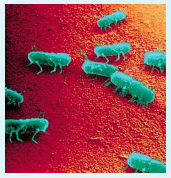


Hippocampus

Saccharomyces cerevisae

Organisms

- **HUMAN**
- **ANIMAL**
- **PLANT**
- **MULTIPLE LIVING CELL**
- **SINGLE LIVING CELL**



Signal transduction

Signaling cells

↓

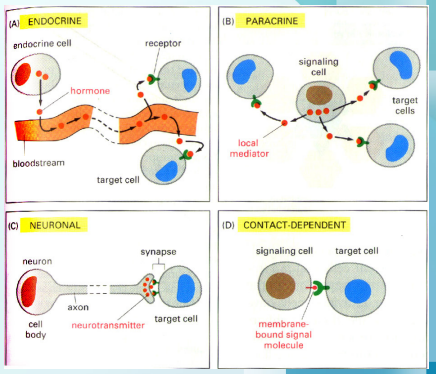
Extracellular signal

↓

Intracellular signal

↓

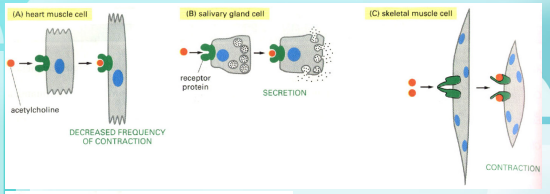
Receptor protien
Target cell

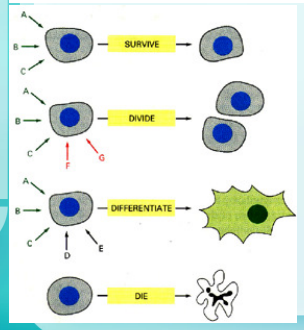


Protein Peptide Amino acid Nucleotide SteroidFatty acid Gas

สัญญาณโมเลกุล	ที่มา	ลักษณะทางเคมี	หน้าที่
ฮอรโมน			
Adrenaline	ต่อมหมวกไต	อนุพันธ์ของ tyrosine	เพิ่มแรงดันเลือด การเต้นของหัวใจ และเมตาบอลิซึม
Cortisol	ต่อมหมวกไต	สเตียรอยด์	มีผลต่อเมแทบอลิซึมของโปรตีน คาร์โบไฮเดรต และไขมัน
Estradiol	รังไข่	สเตียรอยด์	กระตุ้นการพัฒนาการของเพศหญิงในระยะที่สอง
Glucagon	a-cell ของตับอ่อน	เปปไทด์	กระตุ้นการสังเคราะห์กลูโคส การสลายไกลโคเจน และไขมันในเซลล์ตับและเซลล์ไขมัน
Insulin	b-cell ของตับอ่อน	โปรตีน	กระตุ้นการใช้กลูโคส การสังเคราะห์โปรตีนและไขมันในเซลล์ตับ
Testosterone	อัณฑะ	สเตียรอยด์	กระตุ้นเมแทบอลิซึมของเซลล์หลาย ๆชนิด และกระตุ้นการพัฒนาทางเพศขั้นที่สองในเพศชาย
Local mediator			
Epidermal growth factor (EGF)	เซลล์หลาย ๆ ชนิด	โปรตีน	กระตุ้นเซลล์ epidermal และเซลล์อื่น ๆให้มีการแบ่งตัว
Platelet-derived growth factor (PDGF)	เซลล์หลาย ๆชนิด รวมไปถึงเซลล์เกล็ดเลือด	โปรตีน	กระตุ้นเซลล์หลาย ๆชนิดให้มีการแบ่งตัว
Nerve growth factor (NGF)	เซลล์ประสาทหลาย ๆชนิด	โปรตีน	ช่วยส่งเสริมการมีชีวิตรอดของเซลล์ประสาท ทำให้มีการเจริญของ axon
Histamin	Mast cell ในม้าม	อนุพันธ์ของกรดอะมิโน histidine	ช่วยในการขยายของเส้นเลือด เกิดการแดกของเส้นเลือดทำให้เกิดการอักเสบ
Nitric oxide (NO)	เซลล์ประสาทและ endothelial เซลล์ของเส้นเลือด	ก๊าซที่สามารถละลายได้	ทำให้เซลล์กล้ามเนื้อชนิดเรียบมีการพัก (relax) และควบคุมกิจกรรมของเซลล์ประสาท

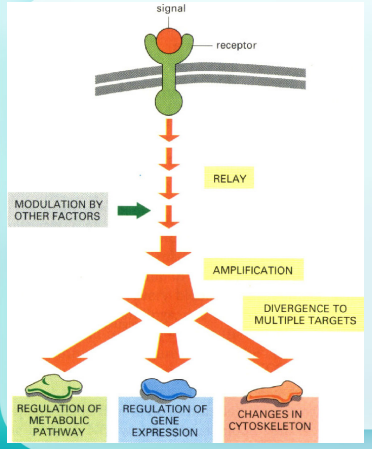
Neurotransmitter			
Acetylcholine	ส่วนปลายของเซลล์ประสาท	อนุพันธ์ของ choline	กระตุ้น neurotransmitter ที่ synapses และการควบคุมระบบประสาทส่วนกลาง
g-Aminobutyric acid (GABA)	ส่วนปลายของเซลล์ประสาท	อนุพันธ์ของกรดกลูตามิค	ยับยั้งการหลั่งของ neurotransmitter ในการควบคุมระบบประสาทส่วนกลาง
Contact-dependent signaling molecules			
Delta	เซลล์ประสาทและเซลล์ตัวอ่อนอื่นๆ	เป็น transmembrane โปรตีน	ทำหน้าที่ยับยั้งเซลล์ข้างเคียงไม่ให้กลายเซลล์พิเศษอย่างเซลล์ที่ทำหน้าที่เป็นเซลล์ที่ให้สัญญาณ





Cell responsive-signaling molecule.

Signaling cascade



Direct signaling

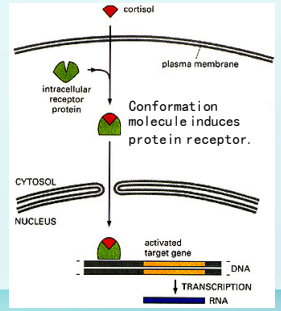
Amplify signaling

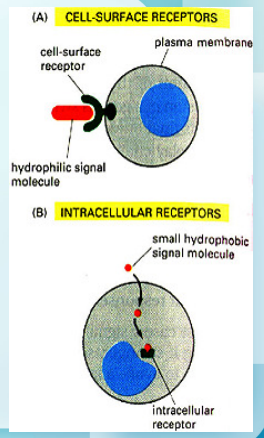
Apparel signaling

Signaling complex

Activation of cytoplamic domain via protein receptors

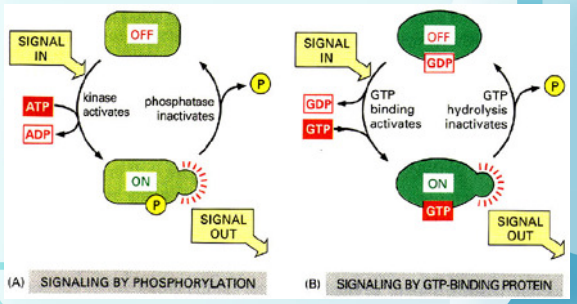
- Hydrophilic molecule
- Hydrophobic molecule





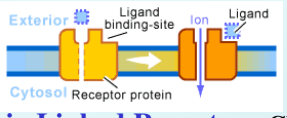
Intracellular signaling molecule: switch on and off

- Protein > Nucleotide > Ion

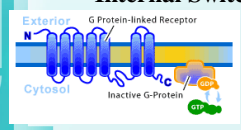


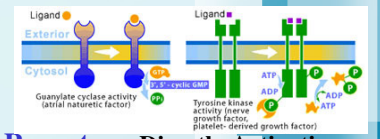
Classification of Cell-Surface Receptors.

1. **Ion-Channel-Linked Receptors:** Converting Chemical Signals to Electrical ones.



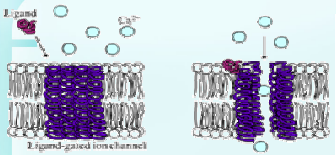
2. **G-protein-Linked Receptors:** Clicking On Internal Switches

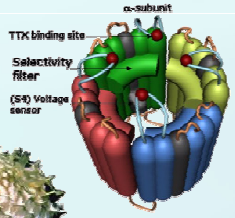


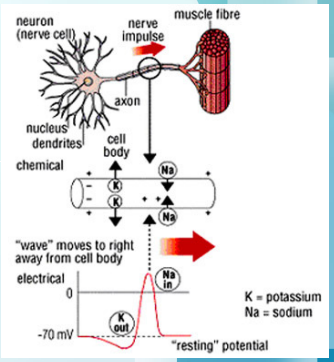


3. **Enzyme-Linked Receptors:** Directly Activating Biochemical Activity

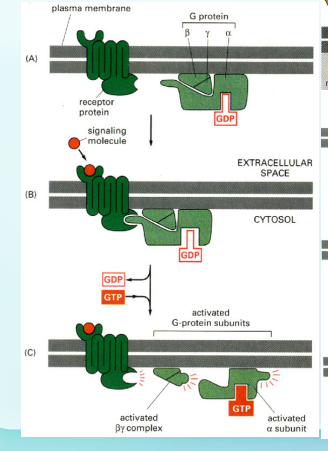
LIGAND-GATED ION CHANNELS

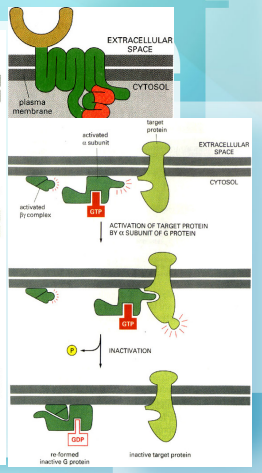


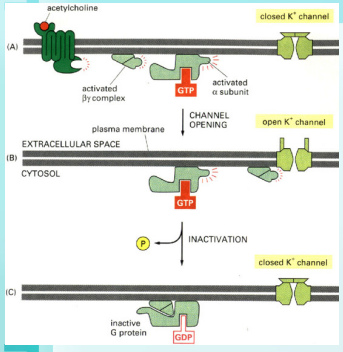


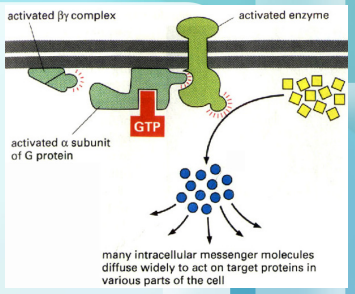


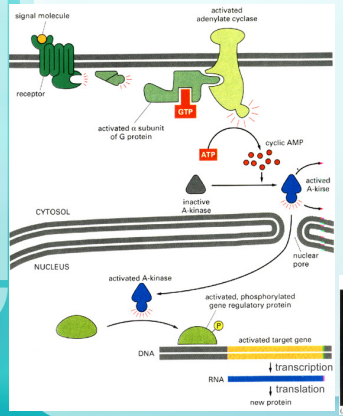
G PROTEIN-COUPLED RECEPTORS

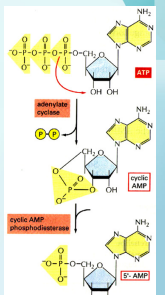


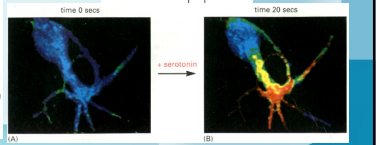


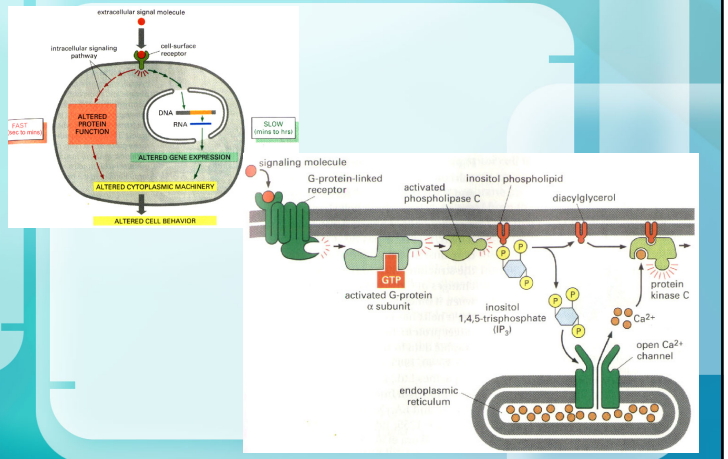












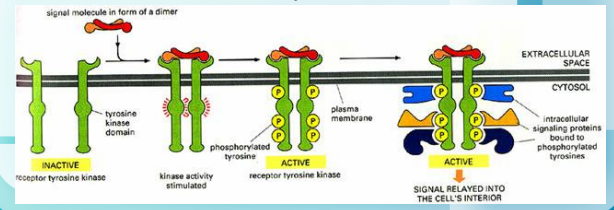
Enzyme-Linked Receptors:

Caenorhabditis elegans

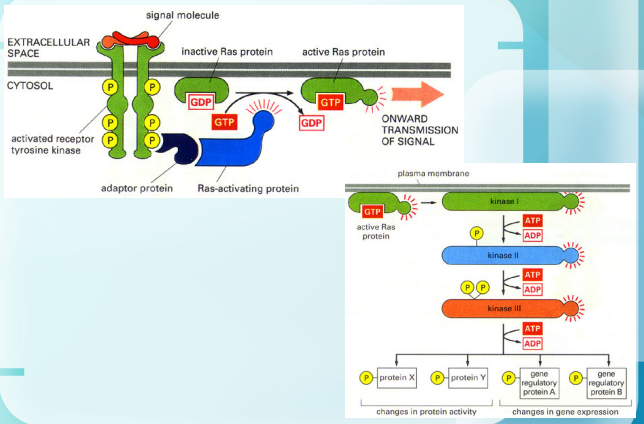
Kinase, Phosphatase, Guanylyl cyclase.

Receptor tyrosine kinases (RTKs)

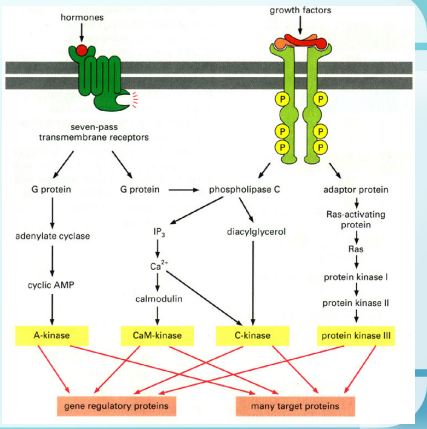
TGFβ



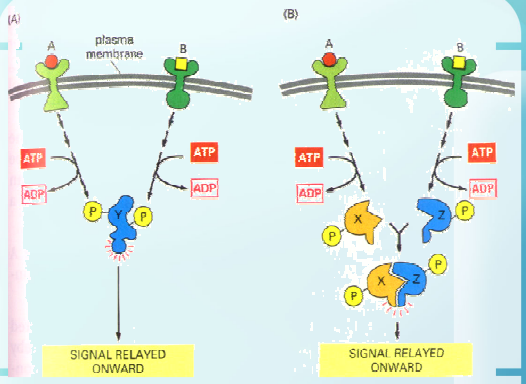
Ras : activated receptor tyrosine kinase



Intracellular signaling pathway

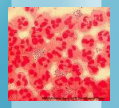


Signal integration



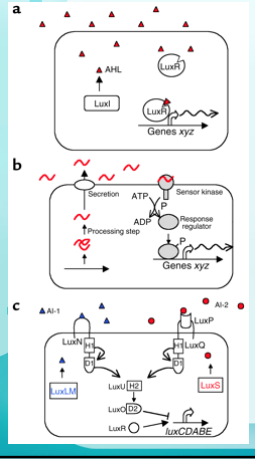
Quorum sensing

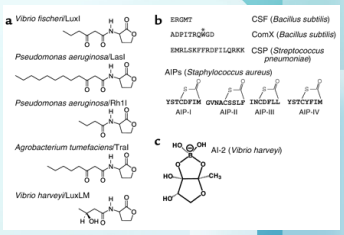
- When bacteria are present in high concentrations.
- One or multiple species.
- Gene expression in response to cell-population density.
- Process: symbiosis, virulence, competence, conjugation, antibiotic production, motility, sporulation, and biofilm. cells secrete molecules

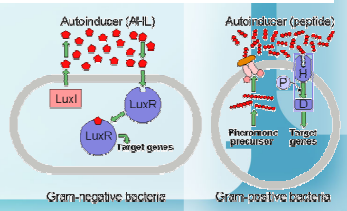


- Horizontal gene transfer increases 10-600X
- Conjugation
- Transfection
- Transduction

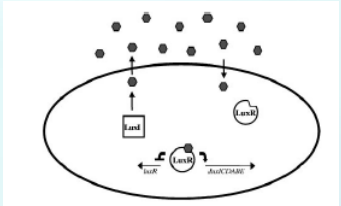
Three canonical quorum-sensing circuits in bacteria and Structures of different bacterial autoinducers.

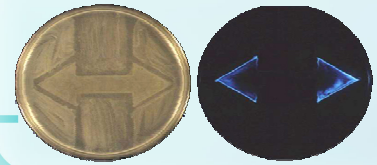


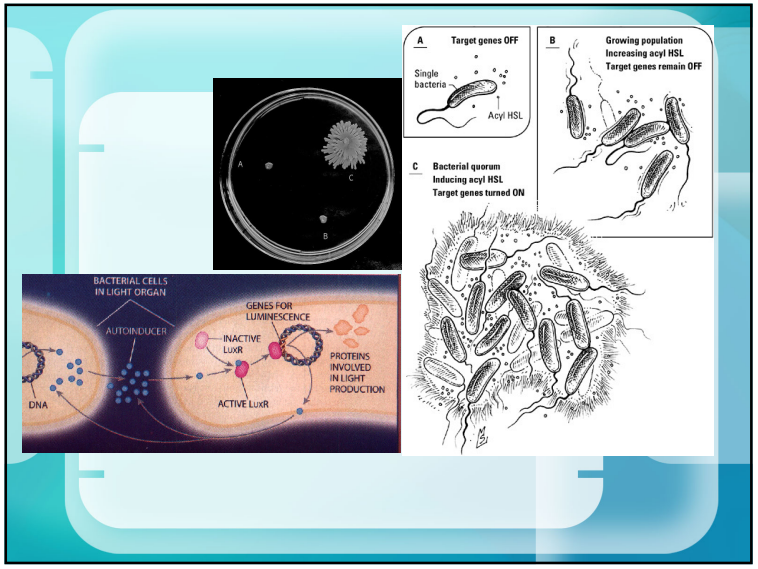




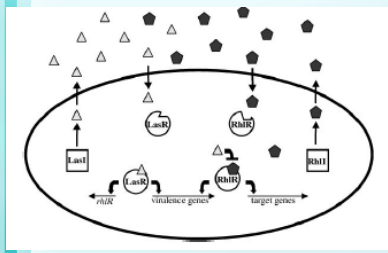
The *Vibrio fischeri* LuxI/LuxR quorum sensing circuit.







The *Pseudomonas aeruginosa* LasI/LasR-RhlI/RhlR quorum sensing system.



N-acyl homoserine lactones

Erwinia carotovora, *Serratia* species

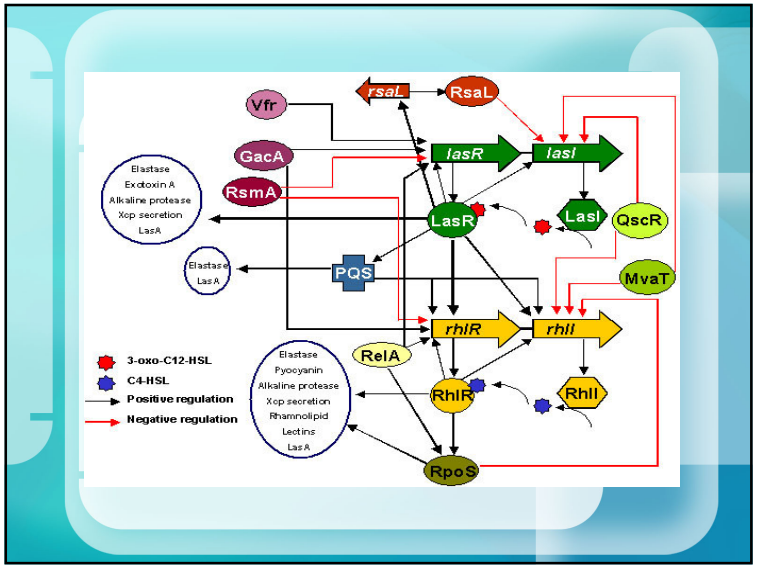


TABLE 1 Organisms possessing LuxI/LuxR homologues: the regulatory proteins, the HSL autoinducers, and the regulated functions[a]

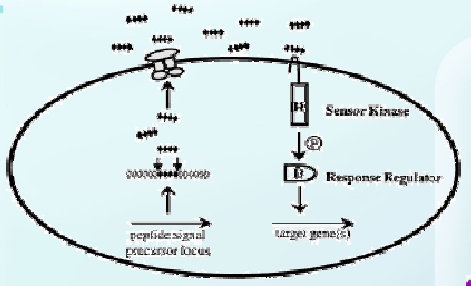
Organism	LuxI/LuxR Homologue(s)	Autoinducer Identity	Target Genes and Functions
Vibrio fischeri	LuxI/LuxR	*N*-(3-oxohexanoyl)-HSL	*hetCTABE* (bioluminescence) (28, 31)
Aeromonas hydrophila	AhyI/AhyR	*N*-butanoyl-HSL	Serine protease and metalloprotease production (154)
Aeromonas salmonicida	AsaI/AsaR	*N*-butanoyl-HSL	*aspA* (exoprotease) (155)
Agrobacterium tumefaciens	TraI/TraR	*N*-(3-oxooctanoyl)-HSL	*tra*, *trb* (Ti plasmid conjugal transfer) (124, 174)
Burkholderia cepacia	CepI/CepR	*N*-octanoyl-HSL	Protease and siderophore production (87)
Chromobacterium violaceum	CviI/CviR	*N*-hexanoyl-HSL	Violacein pigment, hydrogen cyanide, antibiotics, exoproteases and chitinolytic enzymes (14, 96)
Enterobacter agglomerans	EagI/EagR	*N*-(3-oxohexanoyl)-HSL	Unknown (156)
Erwinia carotovora	(a) ExpI/ExpR (b) CarI/CarR	*N*-(3-oxohexanoyl)-HSL	(a) Exoenzyme synthesis, (72, 125) (b) Carbapenem antibiotic synthesis (4)
Erwinia chrysanthemi	ExpI/ExpR	*N*-(3-oxohexanoyl)-HSL	*pecS* (regulator of pectinase synthesis) (103, 132)
Erwinia stewartii	EsaI/EsaR	*N*-(3-oxohexanoyl)-HSL	Capsular polysaccharide biosynthesis, virulence (10)
Escherichia coli	?/SdiA	?	*ftsQAZ* (cell division), chromosome replication (44, 144, 170)
Pseudomonas aureofaciens	PhzI/PhzR	*N*-hexanoyl-HSL	phz (phenazine antibiotic biosynthesis) (123, 171)
Pseudomonas aeruginosa	(a) LasI/LasR	(a) *N*-(3-oxododecanoyl)-HSL	(a) *lasA*, *lasB*, *aprA*, *toxA* (exoprotease virulence factors), biofilm formation (19, 22 and references therein; 114)

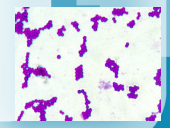
TABLE 1 (*Continued*)

Organism	LuxI/LuxR Homologue(s)	Autoinducer Identity	Target Genes and Functions
	(b) RhlI/RhlR	(b) *N*-butyryl-HSL	(b) *lasB*, *rhlAB* (rhamnolipid), *rpoS* (stationary phase) (22 and references therein; 82, 115)
Rahtonia solanacearum	SolI/SolR	*N*-hexanoyl-HSL, *N*-octanoyl-HSL	Unknown (34)
Rhizobium etli	RaiI/RaiR	Multiple, unconfirmed	Restriction of nodule number (134)
Rhizobium leguminosarum	(a) RhlI/RhiR	(a) *N*-hexanoyl-HSL	(a) *rhlABC* (rhizosphere genes) and stationary phase (18, 51, 133)
	(b) CinI/CinR	(b) *N*-(3-hydroxy-7-*cis*-tetradeceonoyl)-HSL	(b) Quorum sensing regulatory cascade (90)
Rhodobacter sphaeroides	CerI/CerR	7,8-*cis*-*N*-(tetradecanoyl)-HSL	Prevents bacterial aggregation (130)
Salmonella typhimurium	?/SdiA	?	*rck* (resistance to complement killing), ORF on *Salmonella* virulence plasmid (1)
Serratia liquefaciens	SwrI/?	*N*-butanoyl-HSL	Swarmer cell differentiation, exoprotease (30, 47)
Vibrio anguillarum	VanI/VanR	*N*-(3-oxodecanoyl)-HSL	Unknown (97)
Yersinia enterocolitica	YenI/YenR	*N*-hexanoyl-HSL, *N*-(3-oxohexanoyl)-HSL	Unknown (157)
Yersinia pseudotuberculosis	(a) YpsI/YpsR	(a) *N*-(3-oxohexanoyl)-HSL	Hierarchical quorum sensing cascade regulating bacterial aggregation and motility (3)
	(b) YtbI/YtbR	(b) *N*-octanoyl-HSL	

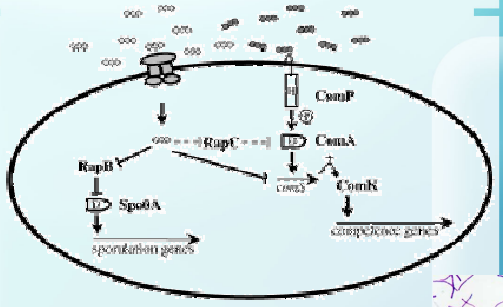
[a]Much of the information in this table comes from (22) with permission.

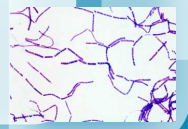
Two component signal transduction in Gram positive bacteria



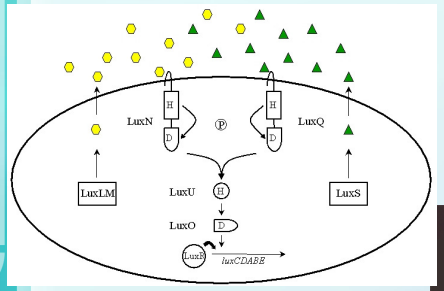


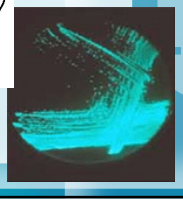
Quorum sensing control of competence and sporulation in *Bacillus subtilis.*





QUORUM SENSING IN *VIBRIO HARVEYI* : A HYBRID HOMOSERINE LACTONE/TWO-COMPONENT SIGNALING CIRCUIT





Interspecies Communication and the LuxS Family of AI-2 Synthases

AI1 → AIS to AIS

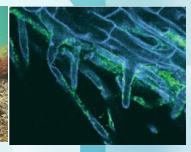
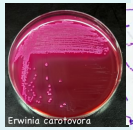
AI2 → AIS to DTAC

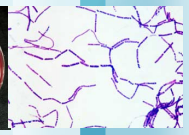
INTERGENERA AND INTERKINGDOM COMMUNICATION

- Seaweed *Delisea pulchra* possess natural agents that counteract quorum sensing in the bacterium *Serratia liquefaciens*.
- *B. subtilis* produces AiiA that is homologous to zinc-binding metallohydrolases

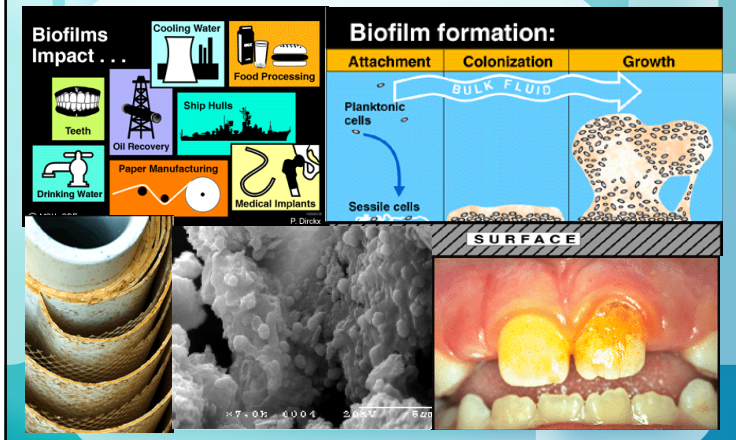
↓

inactivates the *E. carotovora* HSL autoinducer.

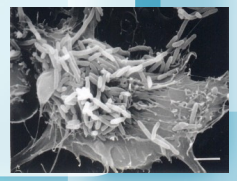


BIOFILM FORMATION



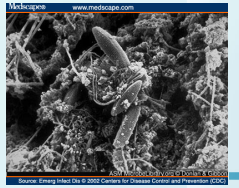
Biofilm (Anton van Leeuwenhoek in 1684)

- Biofilm = a microbial community attached to a surface
- May be one or several organisms
- Sessile organisms: attached
- Planktonic organisms: free living



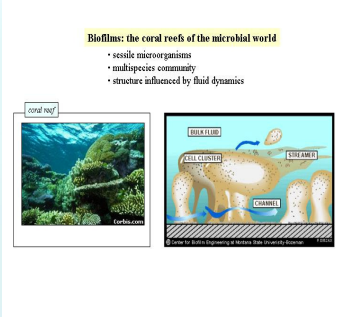
Benefits of Biofilm Formation to Bacteria

- Adherence to hospitable locale
- Syntrophic metabolism
- Horizontal gene transfer
- Disease reservoir



Infectious Disease Biofilms

- Dental plaque
- Endocarditis
- Cystic Fibrosis
- Otitis media
- Urinary catheter
- Implants



Glycocalyx

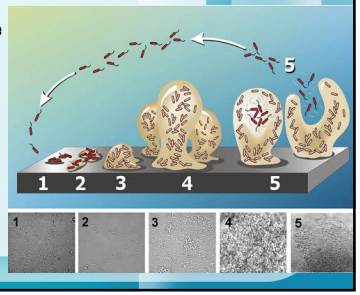
- Complex exopolysaccharides
- Adhesion

Protection from

- biocides
- antibiotics
- bacteriophage
- free-living amoebae
- WBC

Climax Biofilm

- Reaches optimal size
- External organisms become planktonic, leave to colonize elsewhere
- Cells nearest the surface become quiescent or die due to limited O_2 and nutrients, increased waste
- Increased antibiotic resistance



Antimicrobial Resistance

- 10^3-10^4 higher doses of antimicrobials needed to kill biofilm compared with planktonic organisms
- Biofilm is a molecular filter
- Low metabolism of attached cells
- Reduces drug activity

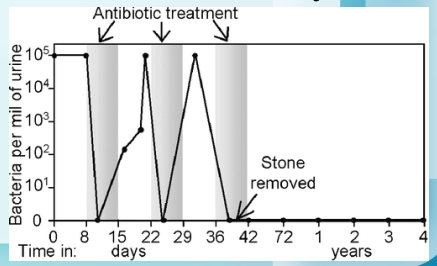
Resistance to Immune System Clearance

- Phagocytosis (macrophages, PMNs)
- surface binding
- engulfed
- killed with digestive enzymes and reactive oxygen molecules (O_2, H_2O_2, NO)

by PMNs

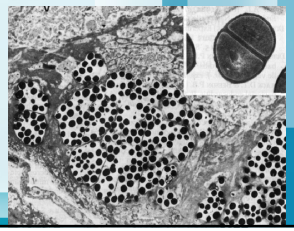
Infectious Kidney Stones

- 15–20% involve urinary tract infection
- Bacterium --> biofilm --> mineralization
- Causative organisms have urease
- urea --> NH_4 + H_2CO_3
- Biofilm concentrates urease --> crystal formation

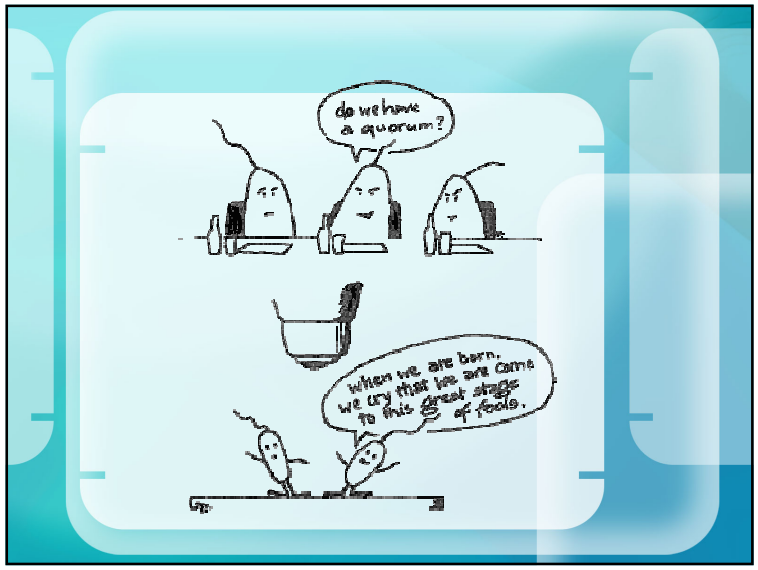


Endocarditis

- Biofilm of bacteria + host components on valve = vegetation
- Requires prior valve injury
- 200X increase in antibiotic resistance
- Rabbit model: block biofilm formation --> acute virulent infection



- Ability of Yersinia pestis to block flea midgut
- Ability of Vibrio cholerae to survive in seawater
- Ability of uropathogenic *E. coli* to block growth of other microbes


do we have a quorum?
When we are born, we cry that we are come to this great stage of fools.