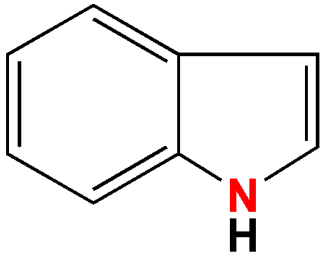
Applications of signaling molecule indole to control biofilm formation and host immunity



Indole as a signaling molecule

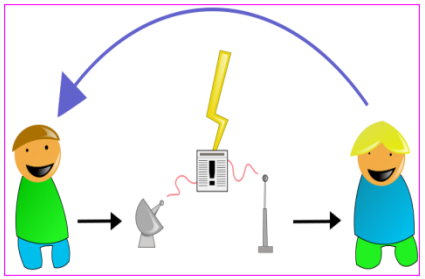
Jintae Lee
Yeungnam University, Korea

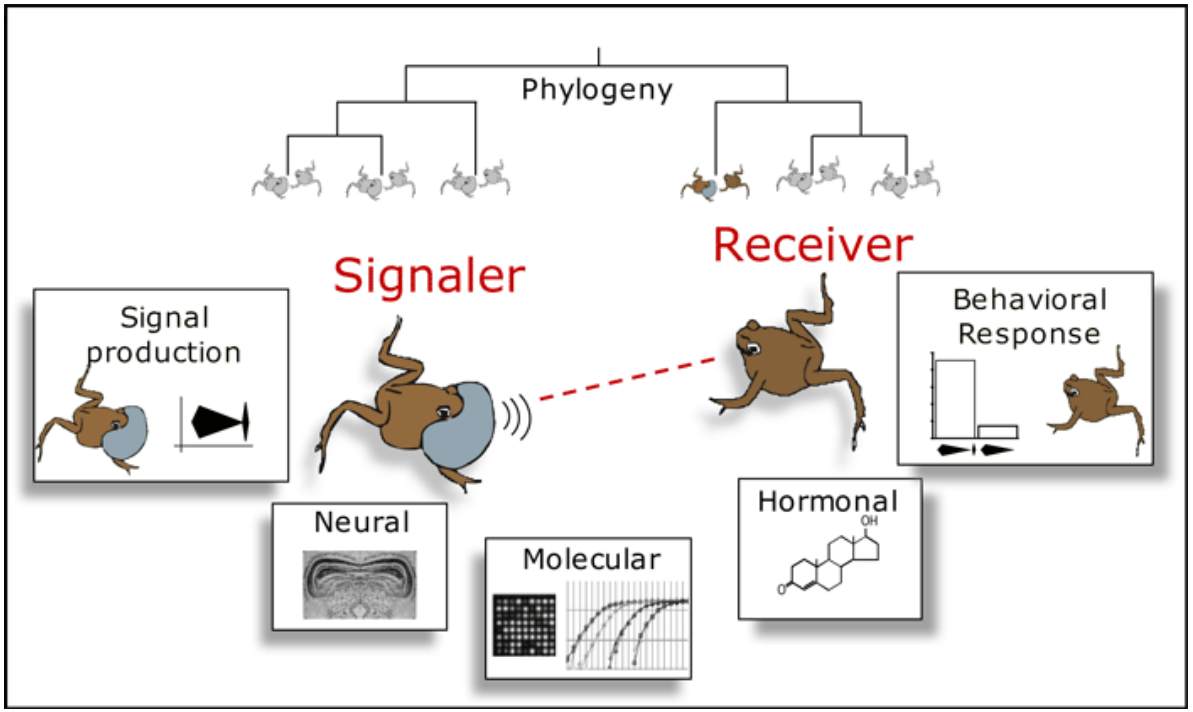
2017. 2. 27.

7th Clinical Microbiology

Animal Communication

영남대학교
Yeungnam University





Bacterial Communication: Quorum Sensing (QS)

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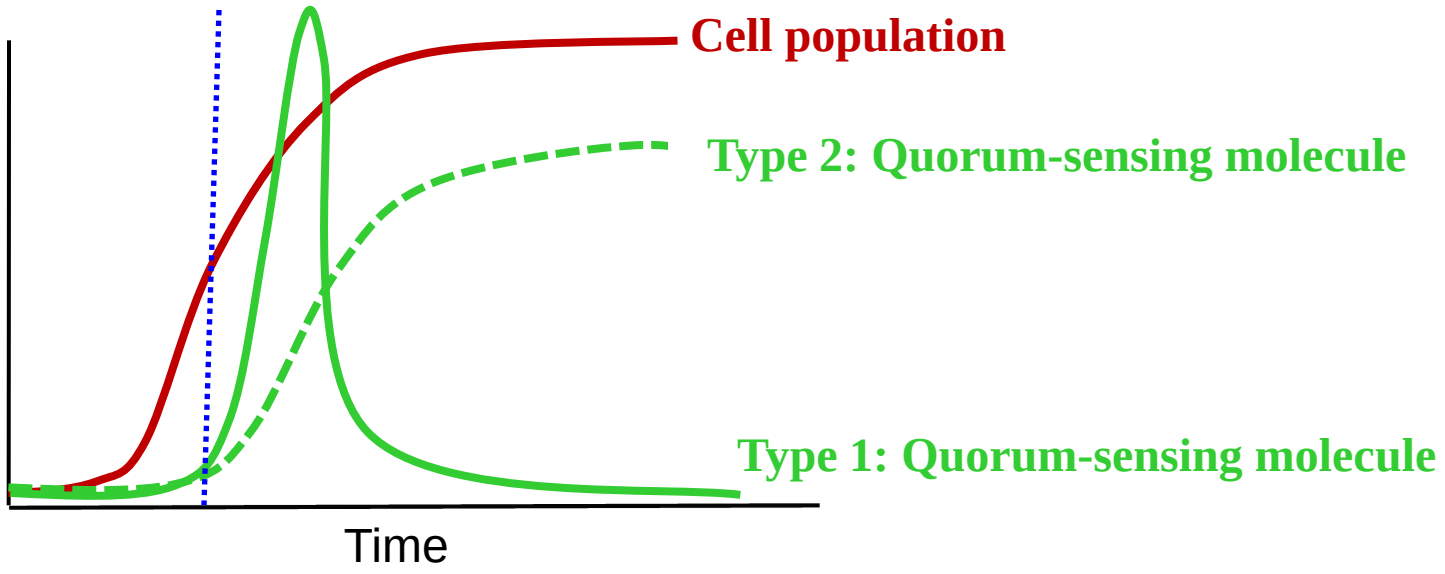
Sensing neighbors

Quorum sensing (bacterial social behavior):

the ability of gene expression regulation in response to increasing cell population density by producing small diffusible chemicals (Fuqua *et al.*, 1994, *J. Bacteriology*)

Quorum-sensing molecule ~ Autoinducer



Why Quorum Sensing (QS)?

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Well-being

To sense and response to environmental stimuli including cell population

Quorum-sensing controlled processes → well-survival !

1) Bioluminescence (symbiosis)

2) Virulence factor production (pathogenesis)

3) Biofilm formation

4) Competence (conjugation)

Bioluminescence (Symbiosis)

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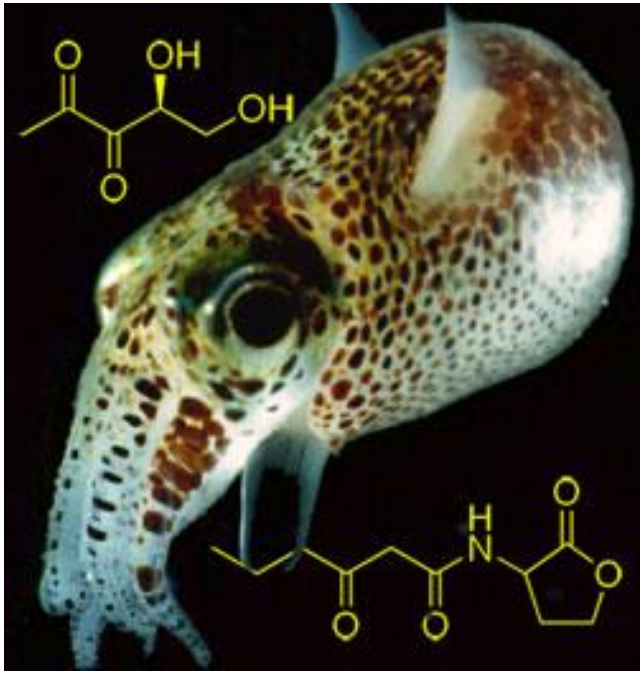
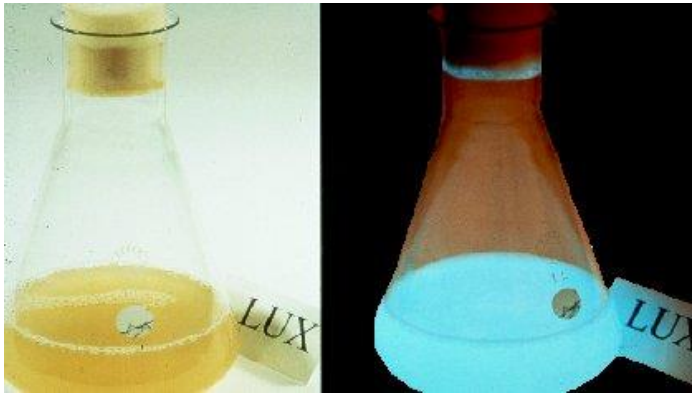


Win-Win



LUX (luminescence phenotype): luciferase

***Vibrio harveyi* in Hawaiian bobtail squid**

Bacteria provide a light to the squid at night and the squid provides a shelter to bacteria

Engebrecht *et al*., 1983, *Cell*

QS Regulates Virulence (Disease)

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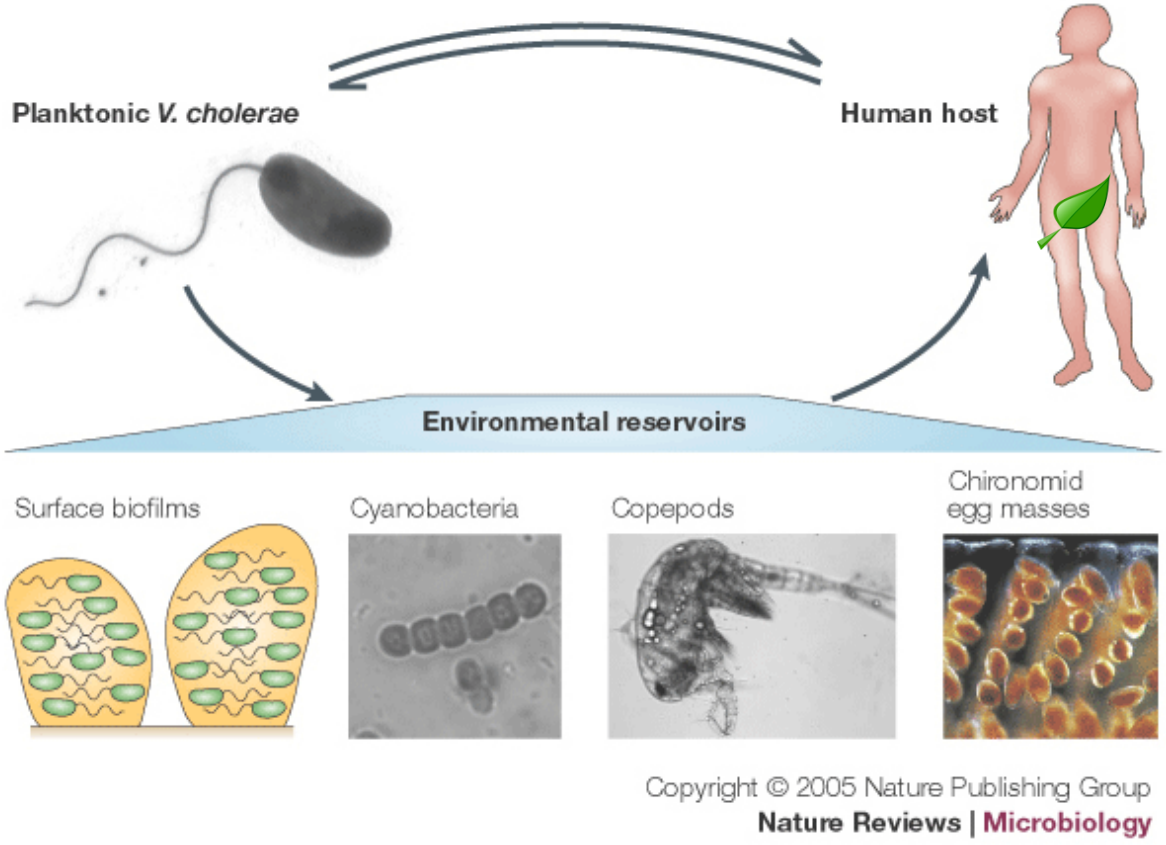
Weapons



QS regulates virulence in *Vibrio cholerae* (Miller *et al.*, 2002, *Cell*)

QS Controls Biofilm Formation

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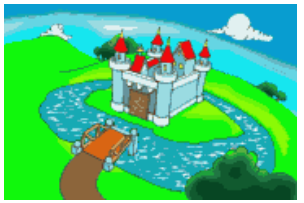
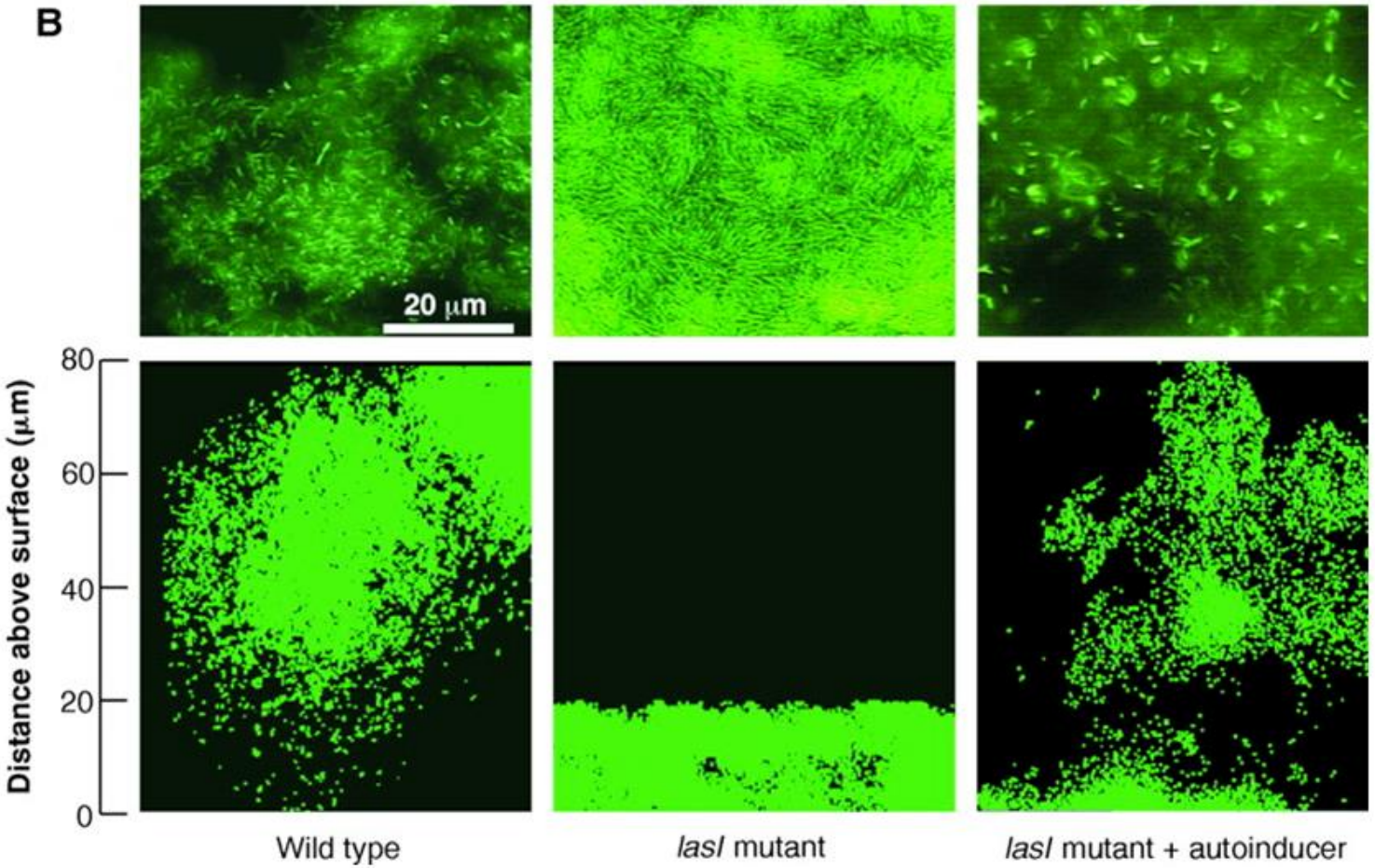
Castles





QS molecules control biofilm formation of *Pseudomonas* (Davies *et al*., 1998, *Science*)

QS Increases Competence (Conjugation)

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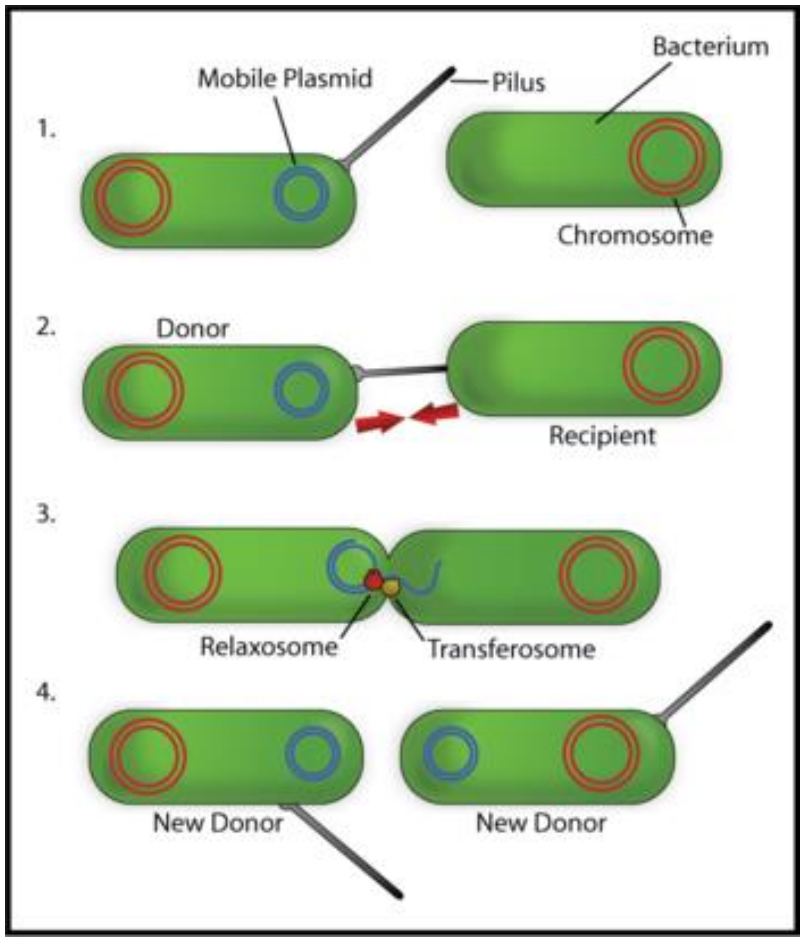
Sex



Mobile plasmid helps bacteria survive in the presence of antibiotics.

Pappas and Winans, 2003, *Mol. Microbiol.*

What Kinds of QS Molecules?

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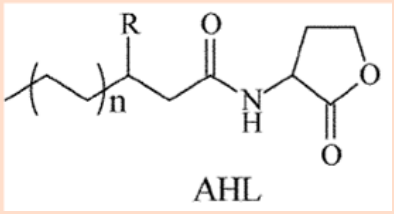
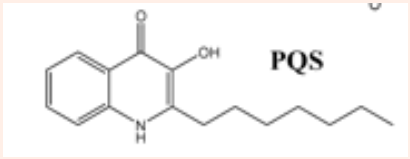
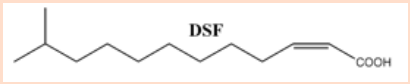
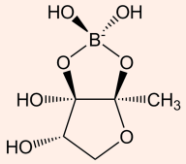
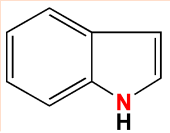
Many languages

Molecules	Structure	Strains	Reference
N-acyl homoserine lactones (AHL)		*Vibrio fisheri* *Pseudomonas aeruginosa*	Gambello *et al.*, 1981, *Cell* Latifi *et al.*, *1991*, *J. Bacteriol.*
Pseudomonas quinolone signal (PQS)		*Pseudomonas aeruginosa*	Pesci *et al.*, *1999*, *PNAS USA*
Diffusible signal factor (DSF)		*Xanthomonas campestris*	Barber *et al.*, 1997, *Mol. Microbiol.*
Autoinducer 2 (AI-2)		Some of Gram-positive and -negative	Chen, *et al.*, 2002 *Nature*
Indole		*Vibrio cholerae* *E. coli*	**Smith, 1897, *J. Exp. Med.***

Interspecies QS Molecule AI-2

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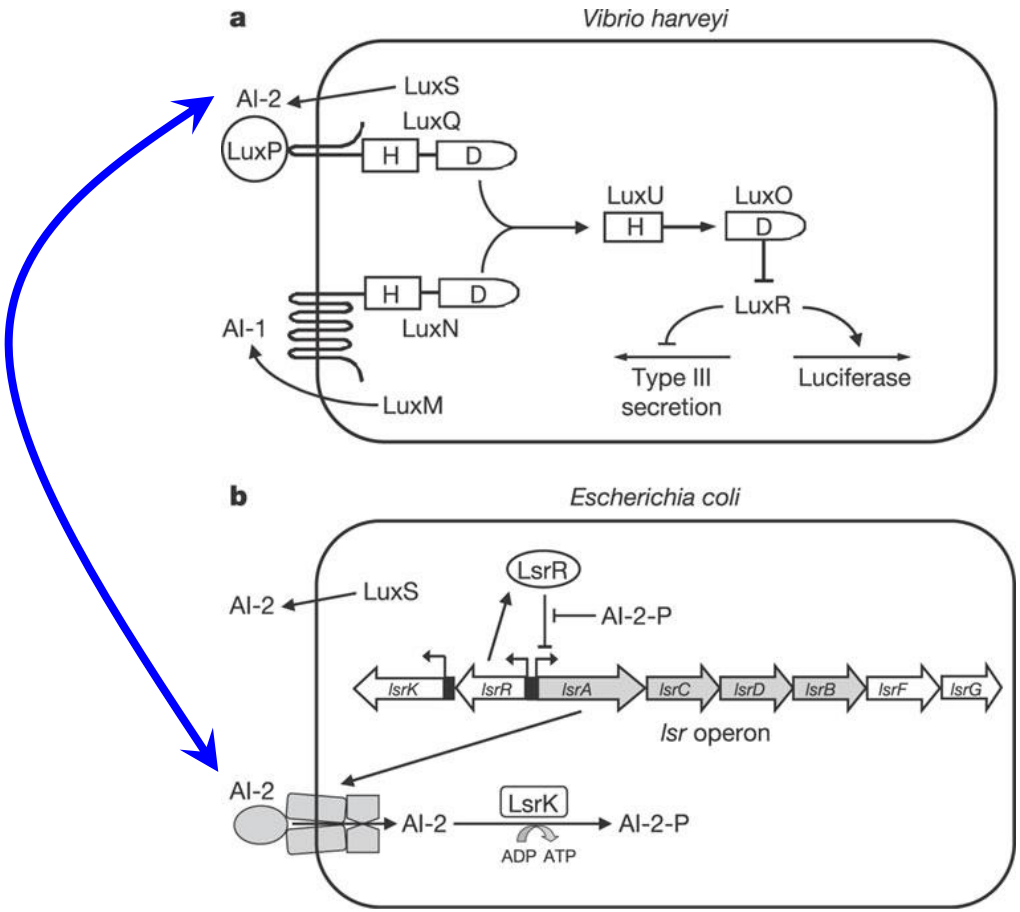
Global language



***E. coli* and *V. harveyi* communicate using AI-2 (Xavier and Bassler, 2005, *Nature*)**

Application of QS: New Type of Antibiotic

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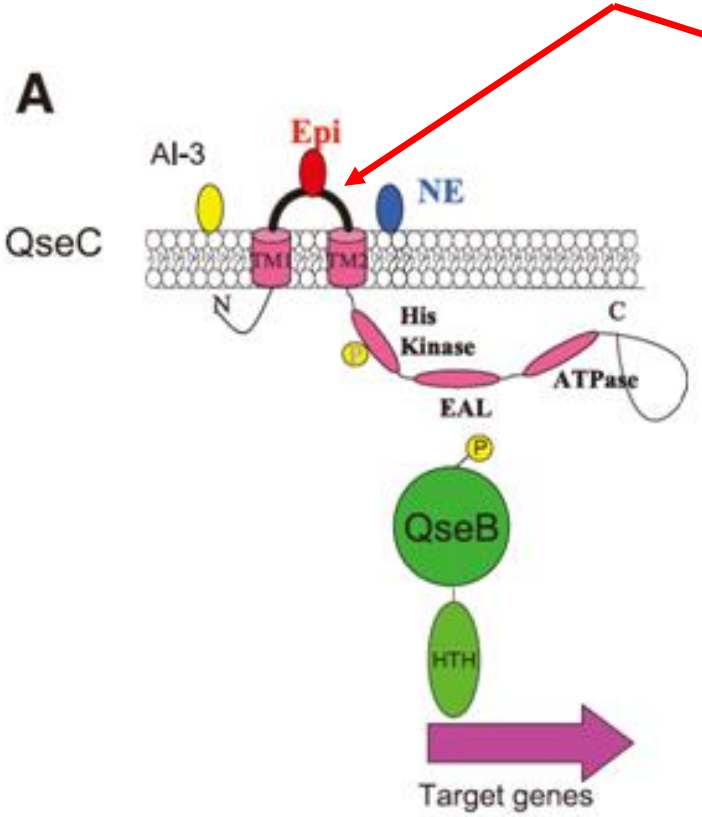
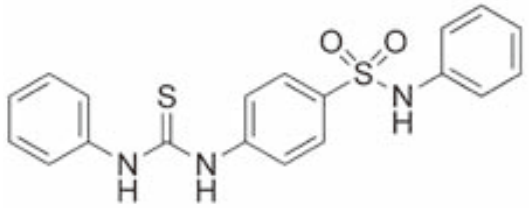
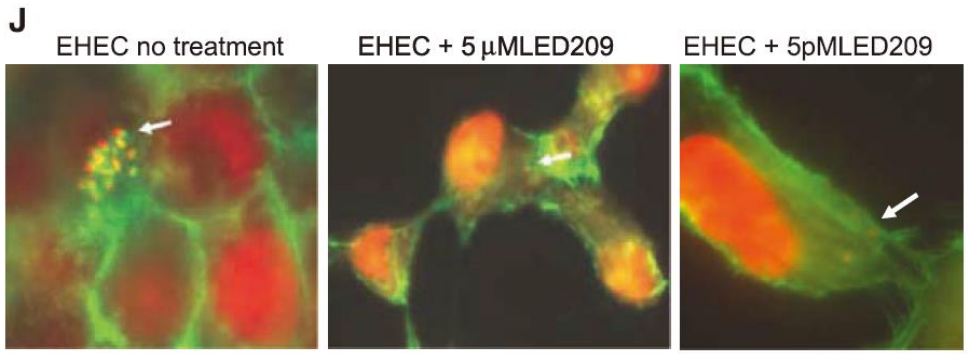
No communication → No disease !





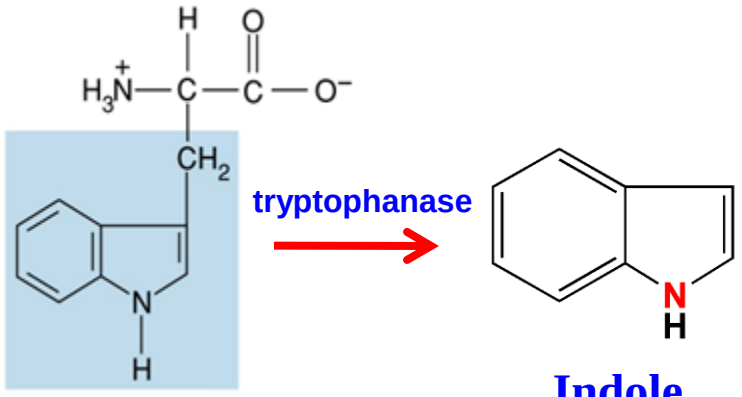
LED209 screened from
a library of 150,000 small organic compounds



An inhibitor of QS sensor kinase decreases virulence of *E. coli* O157: H7

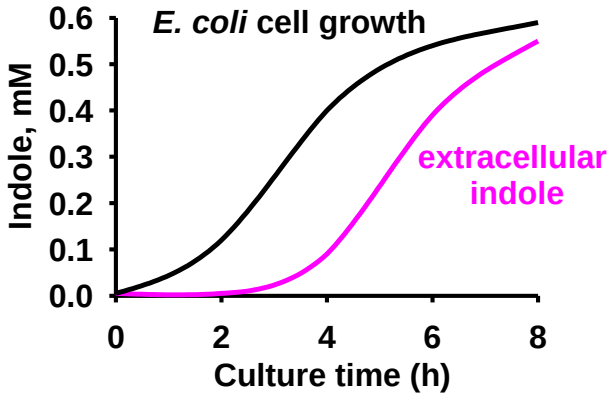
(Rasko *et al.*, 2008, *Science*)

Indole Overview

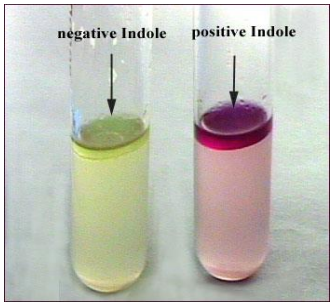


Tryptophan

Indole



A language



- **The average human intestine contains more than 1 kg of bacteria (~100 trillion bacterial cells).**
- ***E. coli* produces a large amount of indole during stationary growth phase (Smith ,1897, *J. Exp. Med.*)**
- **Indole enhances plasmid stability(Chant and Summers, 2007, *Mol. Microbiol*)**
- **Indole increases population-wide antibiotic resistance (Collins *et al*, Nature, 2010 Collins *et al*, Nature Chemical Biology, 2012, Collins *et al*, PNAS 2013)**
- **Prof. Thomas. K. Wood and I have found that indole is a QS molecule during biofilm study.**

Bacterial Biofilm

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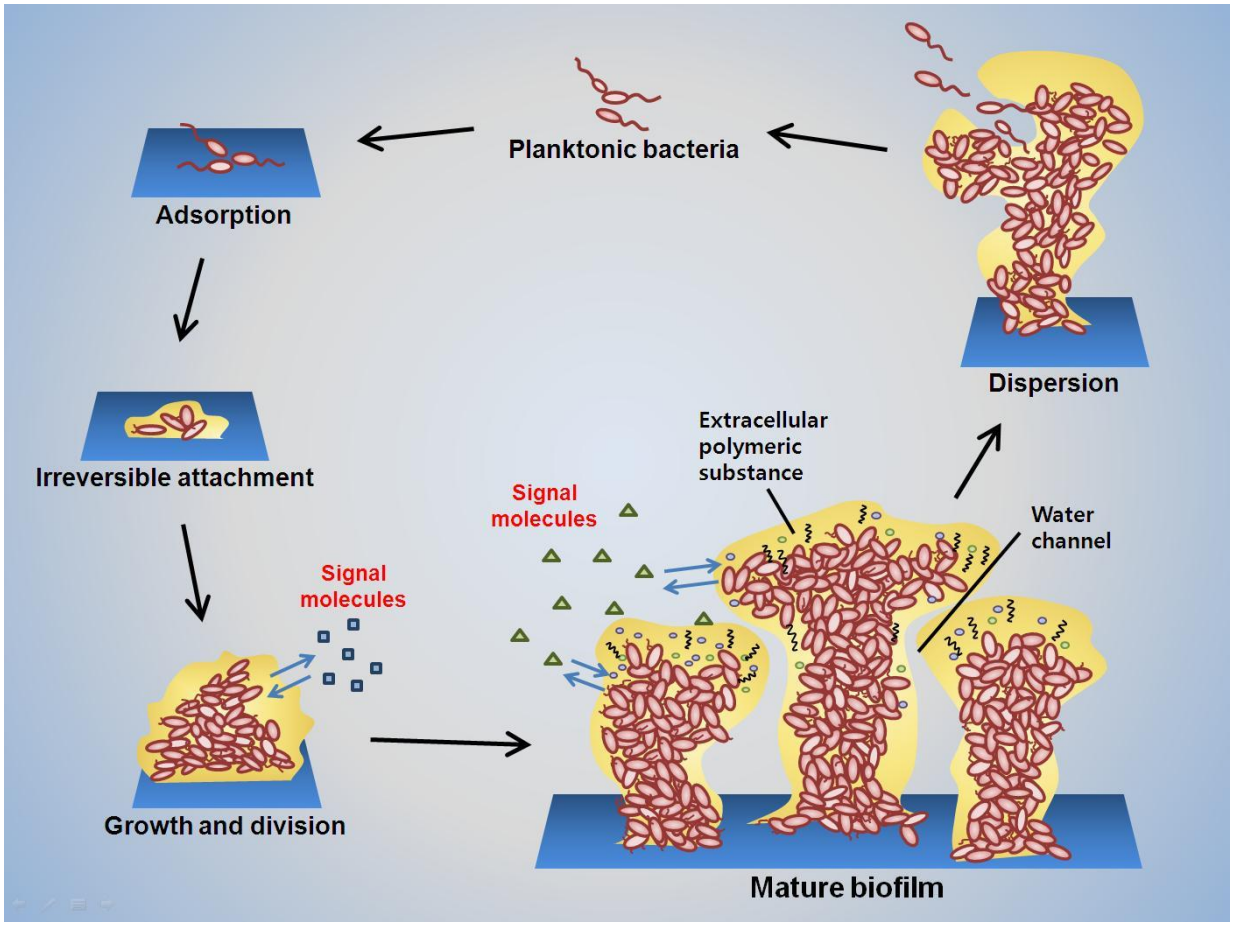
Castle



Bactieral biofilms: a surface attached community of bacteria made of extracellular polymeric substances (carbohydrates, adhesive fibers, eDNA)

Where are Biofilms?

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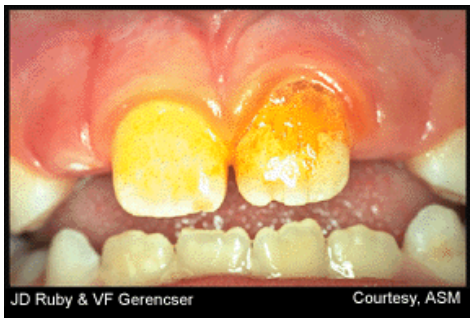
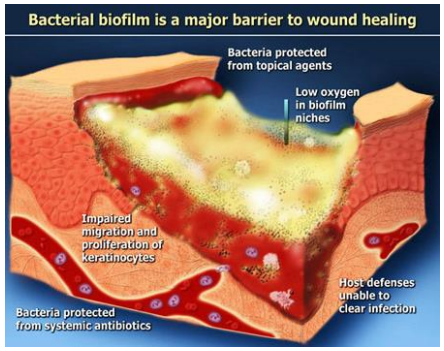
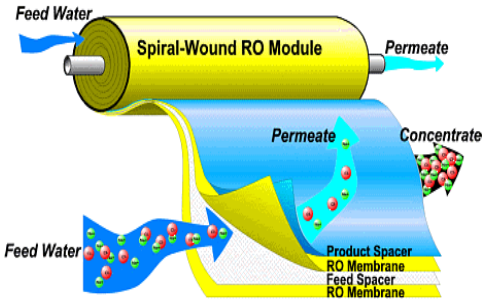
Diverse castles



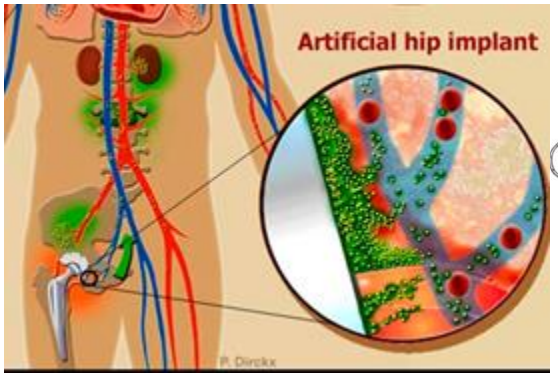
Dental plaque



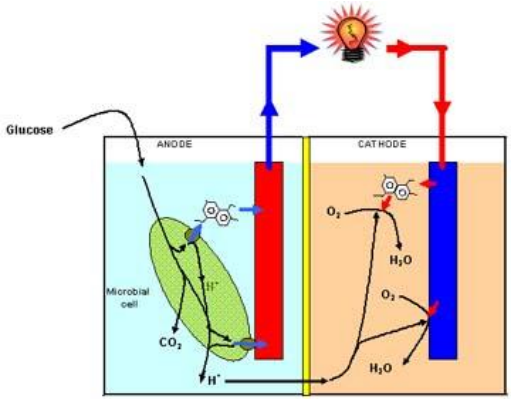
Wound biofilm



Reverse osmosis membrane



Biofilm on medical devices



Microbial fuel cell

99% of bacteria grow as biofilms. Biofilms are important for medicine (80% of bacterial infections occur in biofilms) and engineering (corrosion and bioreactors).

Issue of Biofilm

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- **Biofilm cells can be up to 1000 times more resistant to antibiotic treatment than planktonic (free-floating single cells).**

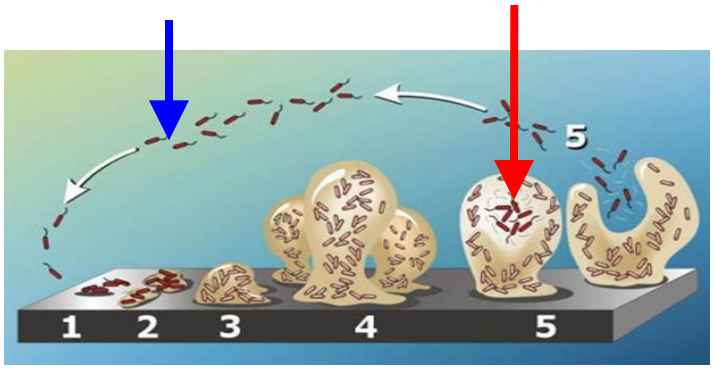
- **Objectives in biofilm research: to discover new biofilm inhibitors and to understand its genetic mechanism.**

- **More than 5000 biofilm papers from PubMed in 2016.**

Very secure castle !

Planktonic cells : easy to kill

Biofilm cells : antibiotic resistant



Methods of Biofilm Reduction

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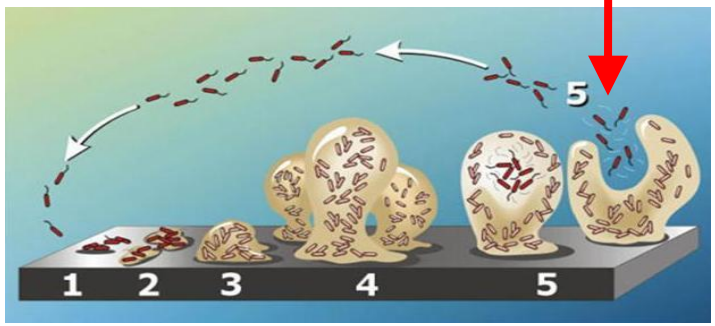
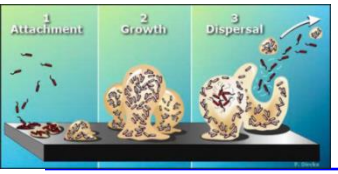
Agents	Target and mechanisms
Protease, DNase, glucosaminidase, chininase, dispersin, etc	Matrix-targeting enzymes
QS modulators	Interference of quorum-sensing (QS)
Small natural molecules	D-amino acids, *cis*-2-decanoic acid, indole, etc
Nitric oxide, DSF	Controlling c-di-GMP
Nutrients (increase or limitation), oxygen, iron, etc	Controlling c-di-GMP
Plant derived compounds (furanons, indole derivatives, flavonoids, etc)	Plant's defense system
Bacterial derived compounds	Possible weapon in bacterial competition
Artificial chemicals or polymers	Surface modification

Biofilm reduction and its mechanism





Biofilm vs. Planktonic in *E. coli*

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biofilm cells  → DNA Microarray Comparison of 4,000 genes ←  planktonic cells

Gene	b#	Expression ratio	Function of the protein
hha	b0460	+25	haemolysin modulating protein
ybaJ	b0461	+36	unknown
yliH	b0836	+3	unknown
yceP	b1060	+4	unknown
ycfR	b1112	+12	stress response protein
ydgG	b1601	+6	AI-2 transporter
b2377	b2377	+12	unknown
b3022	b3022	+8	unknown
hslS	b3686	+32	heat shock protein
hslT	b3687	+4	heat shock protein
soxS	b4062	+49	regulation of superoxide response regulator

My observation : pink mutants produced less indole (↓) and formed more biofilm (↑).

Ren, Bedzyk, Thomas, Ye, and Wood, *Appl. Microbiol. Biotechnol.* (2004)

E. coli O157:H7

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- **Enterohemorrhagic (EHEC) *E. coli* - food borne pathogen that causes bloody diarrhea and hemorrhagic colitis. Approximately 70,000 infections (USA) and 2,100 hospitalizations with a cost of $405 million (2003 value).**
- **No treatment currently available.**
- ***E. coli* O157:H7 makes strong biofilm on any surface.**

Indole and Hydroxyindoles Control EHEC Biofilm

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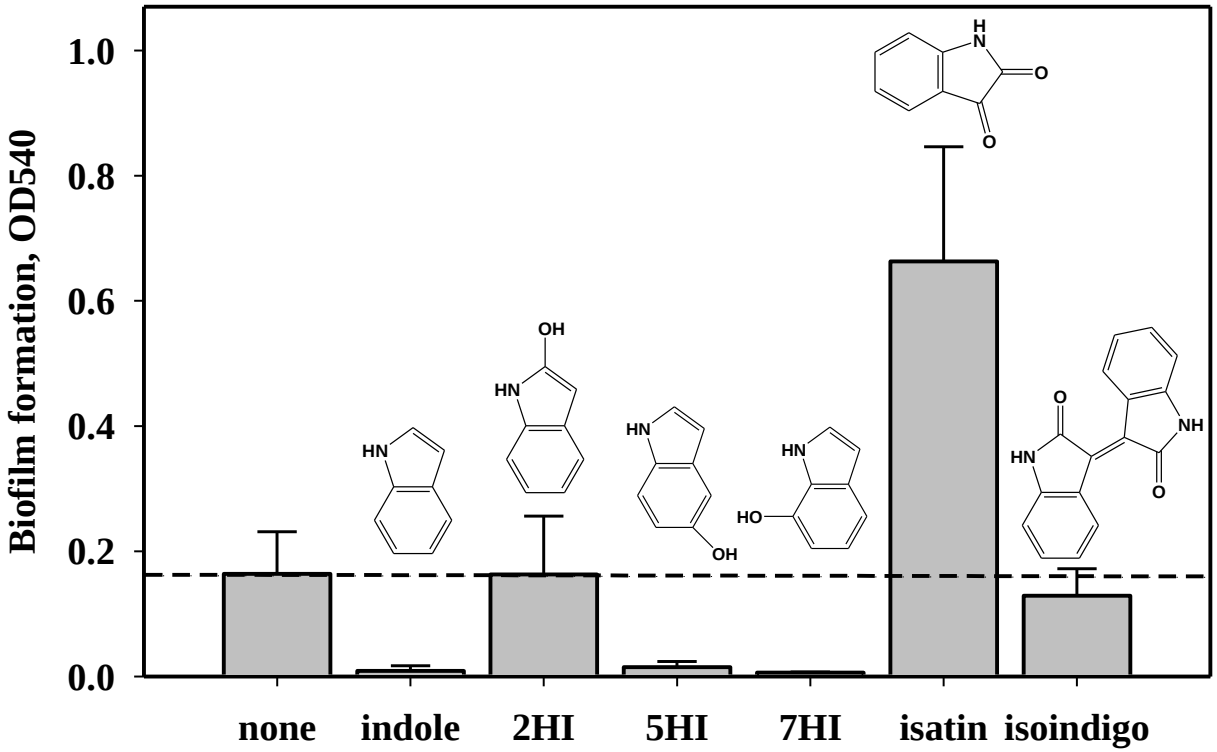
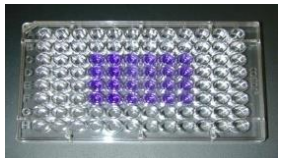
Sophistication of words





Result: **Indole, 5-HI, and 7-HI decrease biofilm formation at 30°C for 7 hrs. Oxidation position is important for controlling biofilm formation.**

Lee, Bansal, Jayaraman, Bentley, and Wood, *Appl. Environ. Microbiol.* (2007)

In Continuous Flow Chamber

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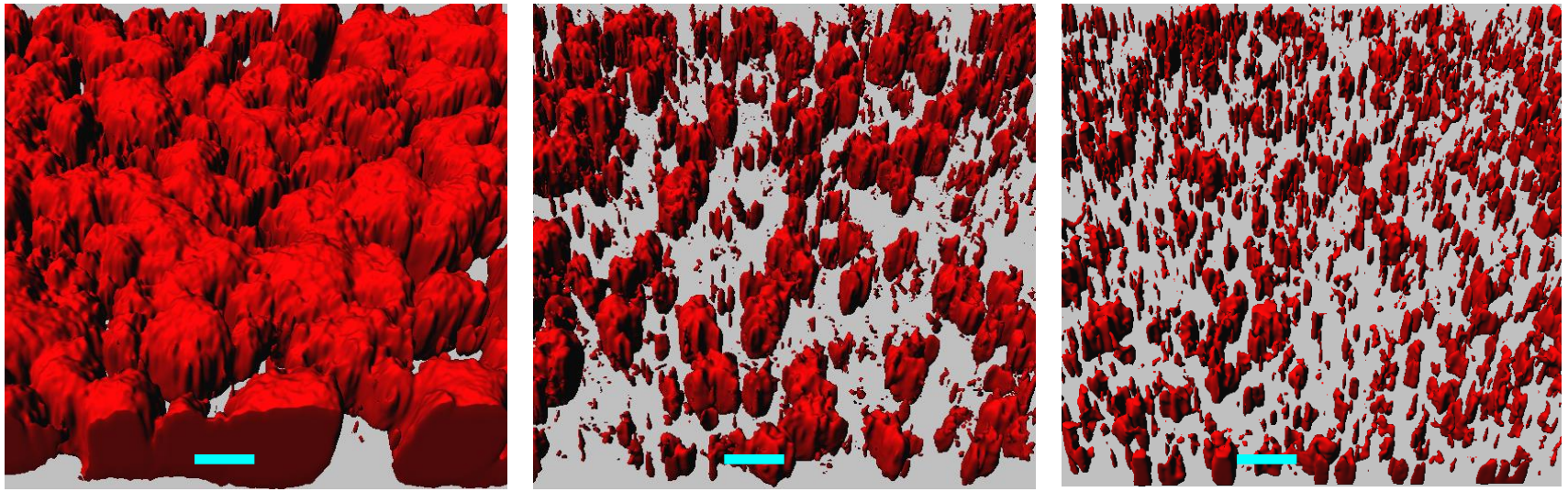
None | 1.0 mM indole | 1.0 mM 7-hydroxyindole



E. coli **O157 biofilm formation in LB at 30°C after 24 hr in continuous flow chambers. Scale bar indicates 20 μm.**

Results: **Confirmed the results in continuous flow chambers..**

Indole Controls Many Genes

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Gene	b #	Fold-change *yceP* + indole	Fold change *Δ trpE*	Fold change *ΔtnaA*	Description
Transcription					
sdiA	*b1916*	2.9	1.0*	1.2	transcriptional activator for cell division (LuxR/UhpA family)
soxS	*b4062*	2.3	2.8	-1.2	regulation of superoxide response regulon
cspA	*b3556*	1.8	-4.6	-1.2*	cold shock protein 7.4, transcriptional activator of hns
Cell motility and secretion					
hha	*b0460*	4.9	-1.4	-1.4	haemolysin expression modulating protein
ybaJ	*b0461*	5.2	-1.1*	1.0*	conserved hypothetical protein
mqsR	*b3022*	2.8	1.1*	1.4	master regulator of chemotaxis via AI-2; interacts with QseB
Colanic acid synthesis genes					
ypdI	*b2376*	1.1*	1.3*	-2.5	YpdI colanic acid synthesis lipoprotein
Acid resistance					
gadE	*b3512*	-5.3	-1.6	1.1*	activator acid resistance genes and putative LuxR transcriptional activator
gadA	*b3517*	-4.9	-2.3	1.2*	glutamate decarboxylase A, isozyme, PLP-dependent
gadB	*b1493*	-3.3	-2.6	1.2*	glutamate decarboxylase isozyme
gadC	*b1492*	-3.7	-1.6	1.2*	acid sensitivity protein, putative transporter
hdeA	*b3510*	-4.6	-2.3	1.0*	periplasmic chaperone of acid-denatured protein
hdeB	*b3509*	-4.3	-2.3	1.2*	10K-L protein, pereplasmic protein related to acid resistance protein
hdeD	*b3511*	-2.6	-1.6	-1.5	protein involved in acid resistance
ymgC	*b1167*	-2.3	1.2*	1.5	hypothetical protein
ymgA	*b1165*	-3.3	1.1	1.7	hypothetical protein
ymgB	*b1166*	-6.1	1.2	1.5	hypothetical protein
Phage-related genes					
ypjF	*b2646*	1.2*	1.2*	-12.1	CP4-57 prophage
ymfI	*b1143*	1.0*	1.1*	-5.7	e14 prophage
ydaY	*b1366*	1.0*	1.0*	-4.6	Rac prophage

Result: Indole influences gene expression of cell motility and the acid resistance genes.

Lee, Jayaraman, and Wood, *BMC Microbiology* (2007, >290 citations)

Indole against Other Species

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Yeungnam University

Defense against other species

Hypothesis: indole as a defense system in multispecies nature.

- **System: pathogenic *Pseudomonas aeruginosa* + Indole**

- ***P. aeruginosa* is a notorious human pathogen that can cause chronic infection in the lungs, ears, wounds, and burns. It easily acquires antibiotic resistance. No production of indole**

- ***P. aeruginosa* produces various toxic chemicals for human and other bacteria.**

Reduction of Toxins by Indole

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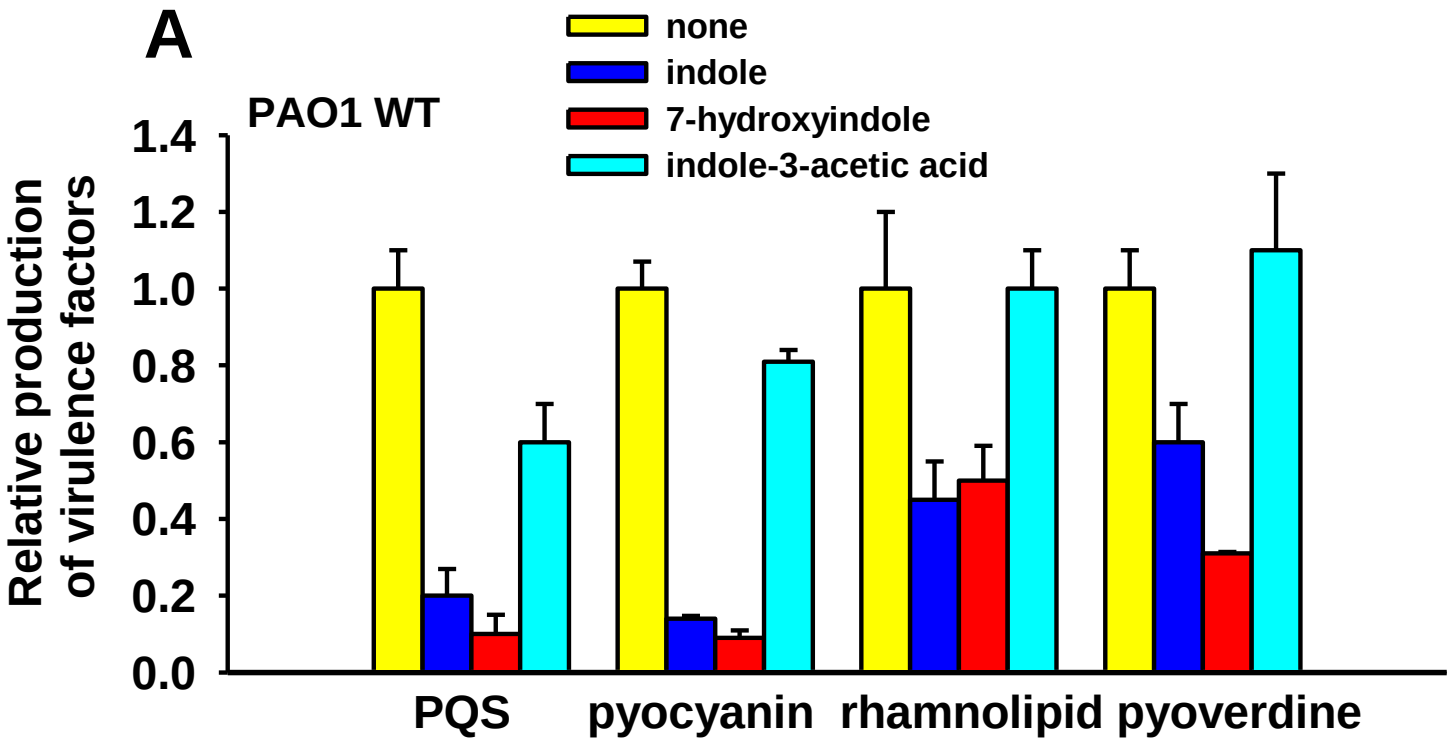
Defense tools



Result: **indole and 7-HI decreased the production of virulence factors without affecting cell growth. Maybe, *E. coli* utilizes indole to compete against *P. aeruginosa*.**

Mechanism of Indole in *P. aeruginosa*

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PA#	Gene	Fold change[1] indole vs. no indole	Fold change[1] 7HI vs. no 7HI	Description
Multidrug efflux transporter				
PA4205	*mexG*	**-13.0**	**-7.0**	Hypothetical protein, part of the *mexGHI-opmD* cluster
PA4206	*mexH*	**-11.3**	**-5.7**	Efflux membrane fusion protein precursor
PA4207	*mexI*	**-6.1**	**-4.0**	Efflux transporter
PA4208	*opmD*	**-7.5**	**-4.6**	Probable outer membrane efflux protein
Phenazine synthesis				
PA1902	*phzD2*	**-3.2**	**-3.0**	Phenazine biosynthesis protein PhzD
PA1903	*phzE2*	**-3.5**	**-2.6**	Phenazine biosynthesis protein PhzE
PA1904	*phzF2*	**-4.0**	**-4.3**	Phenazine biosynthesis protein
PA1905	*phzG2*	**-3.2**	**-3.2**	Pyridoxamine 5'-phosphate oxidase
PA2274		**-4.9**	**-3.2**	Phenazine biosynthesis protein
PA4210	*phzA1*	**-2.5**	**-3.7**	Phenazine biosynthesis protein
PA4217	*phzS*	**-2.8**	**-2.8**	Flavin-containing monooxygenase
PQS synthesis				
PA0996	*pqsA*	**-1.9**	**-2.0**	PqsA, probable coenzyme A ligase
PA0997	*pqsB*	**-2.3**	**-2.5**	PqsB,
PA1000	*pqsE*	**-2.0**	**-2.1**	PqsE, quinolone signal response protein
PA1003	*mvfR*	1.3	-1.1	MvfR (PqsR), PQS transcriptional regulator
Pyoverdine synthesis				
PA2393	*pvdM*	**-2.5**	-1.1	pyoverdine biosynthesis protein PvdM
PA2394	*pvdN*	**-2.5**	-1.2	pyoverdine biosynthesis protein PvdN
PA2424	*pvdL*	**-2.3**	-1.3	pyoverdine biosynthesis protein PvdV
PA2426	*pvdS*	**-6.1**	**-2.6**	Sigma factor PvdS, transcriptional regulator
Metabolism				
PA0283	*sbp*	**-8.6**	-1.7	Sulfate-binding protein precursor
PA1838	*cysI*	**-6.1**	**-2.1**	Sulfite reductase
PA3441	*ssuF*	**-7.5**	**-5.7**	SsuF, part of the *ssu* locus,
PA3442	*ssuB*	**-4.6**	**-2.6**	SsuB, part of the *ssu* locus
PA3443	*ssuC*	**-3.2**	**-2.6**	SsuC, part of the *ssu* locus
PA3444	*ssuD*	**-6.1**	**-2.1**	SsuD, part of the *ssu* locus
PA3445	*ssuA*	**-6.5**	**-2.8**	SsuA, part of the *ssu* locus
PA3446	*ssuE*	**-6.5**	-1.6	SsuE, part of the *ssu* locus
PA4442	*cysN*	**-4.6**	**-2.0**	ATP sulfurylase GTP-binding subunit
PA4443	*cysD*	**-4.9**	-1.7	ATP sulfurylase small subunit
PA5025	*metY*	**-2.6**	-1.3	Homocysteine synthase
PA5427	*adhA*	**2.1**	**2.6**	Alcohol dehydrogenase
Motility and TypeIV pilus				
PA2131		-1.9	**-2.6**	Probable pili assembly chaperone
PA2570	*paIL*	1.6	**-2.8**	PA-I galactophilic lectin
PA4084	*cupB3*	**-2.8**	**-4.0**	Probable fimbrial biogenesis usher protein
PA4085	*cupB2*	**-3.0**	**-2.1**	Probable pili asembly chaperone
PA4297	*tadG*	**2.3**	**3.5**	TadG
PA4299	*tadD*	1.7	**-2.6**	Flp pilus assembly protein TadD
PA4300	*tadC*	1.7	**-2.3**	Flp pilus assembly protein TadC
PA4301	*tadB*	1.6	**-3.0**	Flp pilus assembly protein TadB
PA4302	*tadA*	1.9	**-2.5**	Flp pilus assembly protein, ATPase CpaF
PA4303	*tadZ*	1.7	**-2.3**	Flp pilus assembly protein, ATPase CpaE
PA4304	*rcpA*	**2.0**	-1.9	Flp pilus assembly protein, secretin CpaC
PA4651		**2.0**	**-3.5**	Probable pili assembly chaperone
Transport of small molecules				
PA1108		-1.9	**-5.7**	Probable MFS transporter
PA2092		**-2.6**	**-4.0**	Probable MFS transporter
PA2204		**-9.8**	-1.9	Binding protein component of ABC transporter
PA2328		**-6.1**	**-5.3**	Hypothetical protein in the cluster of ABC transporter
PA2329		**-5.7**	**-5.7**	Probable ATP-binding component of ABC transporter
PA2330		**-4.9**	**-4.3**	Hypothetical protein in the cluster of ABC transporter
PA2331		**-5.7**	**-4.0**	Hypothetical protein in the cluster of ABC transporter
PA3531	*bfrB*	**3.2**	**2.3**	Bacterioferritin, transport of small molecules
PA3926		-1.7	**-2.0**	Probable MFS transporter
PA4514	*piuA*	**-4.3**	**-2.5**	Probable outer membrane receptor for iron transport
Oxygenases				
PA2512	*antA*	**5.3**	**-2.0**	Anthranilate dioxygenase large subunit
PA2513	*antB*	**6.1**	**-2.6**	Anthranilate dioxygenase small subunit
PA2514	*antC*	**3.0**	**-2.8**	Anthranilate dioxygenase reductase
PA0106	*coxA*	**3.2**	1.4	Cytochrome c oxidase, subunit I
PA0107		**2.8**	1.3	Predicted cytochrome oxidase assembly factor
PA0111		**3.0**	1.3	Hypothetical protein in the cluster of oxidase
PA0112		**3.0**	1.1	Hypothetical protein in the cluster of oxidase
PA0113		**3.0**	1.4	Probable cytochrome c oxidase assembly
Others				
PA0716		**5.7**	**7.0**	Probable bacteriophage protein
PA0740	*sdsA1*	**-8.6**	**-3.0**	Probable beta-lactamase
PA1109		**-2.6**	**-5.7**	Transcriptional regulator
PA3234	*yjcG*	**4.3**	**2.0**	Probable sodium:solute symporter
PA3337	*rfaD*	**2.0**	**2.5**	ADP-L-glycero-D-mannoheptose 6-epimerase
Hypothetical proteins				
PA0284		**-13.9**	-1.6	Hypothetical protein, induced by MvfR
PA0492		**-4.3**	**-3.5**	Hypothetical protein
PA0696		**-4.3**	**-2.5**	Hypothetical protein
PA0939		-1.1	**-5.3**	Hypothetical protein
PA1190		**5.7**	1.6	Hypothetical protein
PA1837		**-4.6**	**-2.1**	Hypothetical protein
PA1914		1.1	**-6.1**	Hypothetical protein
PA1953		**-3.2**	**-6.1**	Hypothetical protein
PA2036		**-2.0**	**-7.0**	Hypothetical protein
PA2078		**-3.0**	**-5.7**	Hypothetical protein
PA2419		-1.6	**6.1**	Hypothetical protein
PA3235		**4.0**	**2.5**	Hypothetical protein
PA3237		-1.9	**-6.1**	Hypothetical protein
PA3719		**4.6**	1.3	Hypothetical protein
PA3931		**-5.3**	-1.7	Hypothetical protein

Result: **Indole and 7-HI prevent bacterial communication of *P. aeruginosa*. quorum quenching!**

Inhibition of Swarming (not Growth) by Indole and 7-HI

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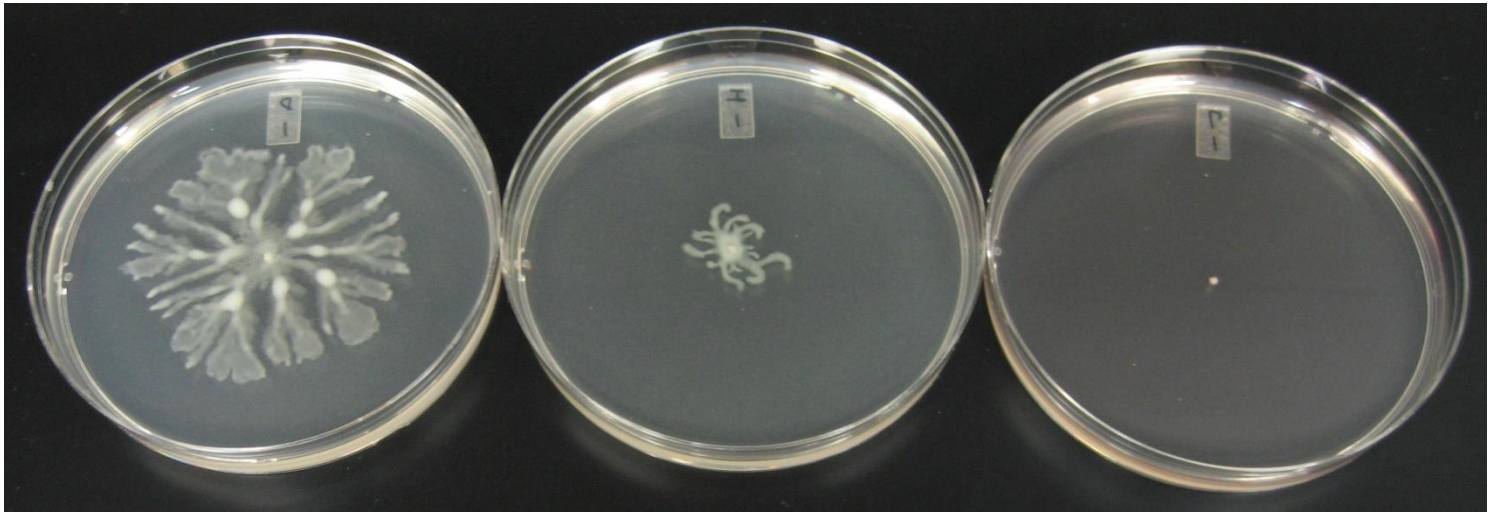
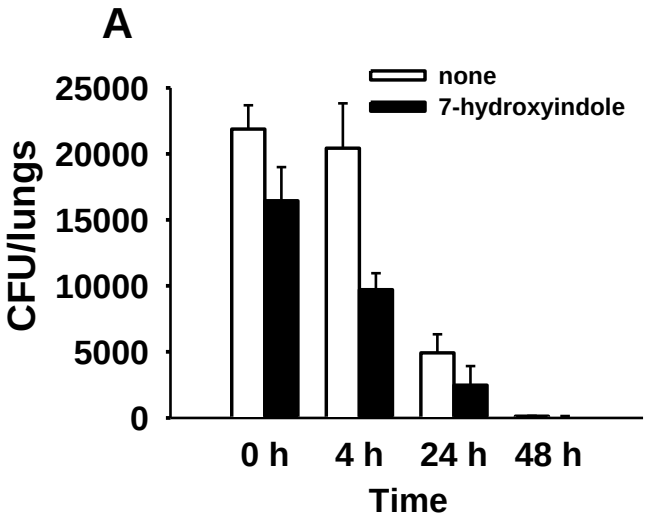
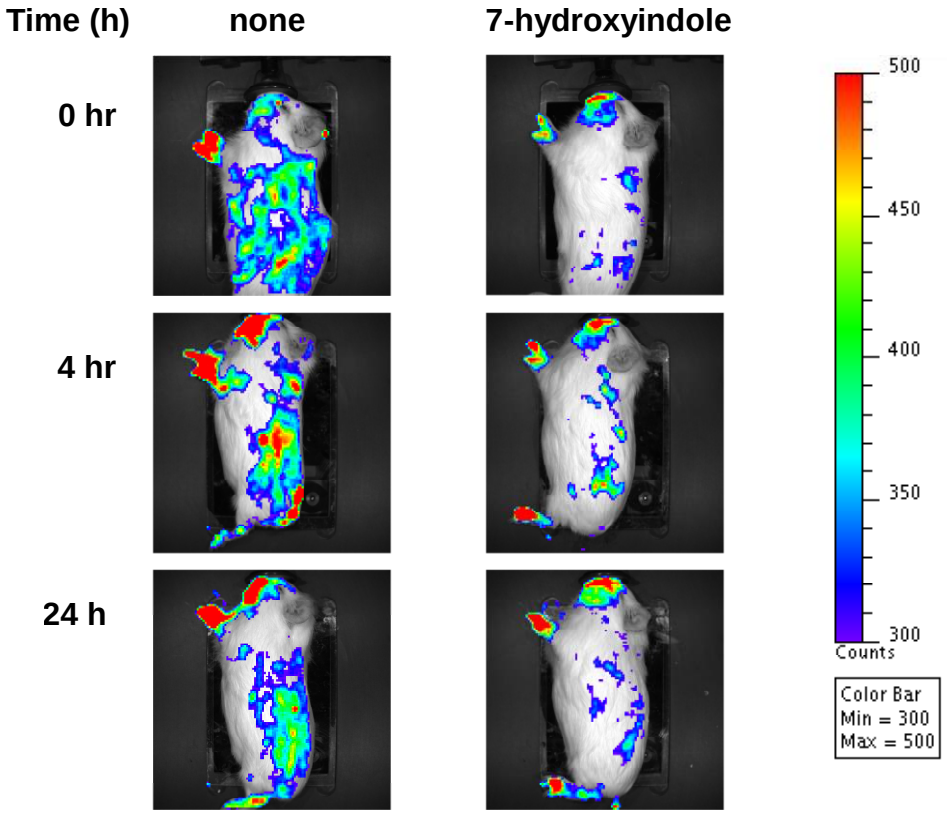
none **indole** **7-hydroxyindole**



Result: **Indole decreases moving and 7-HI stops moving of *P. aeruginosa*..**

Animal Study (Guinea Pigs)





Result: **7-HI reduced attachment of *P. aeruginosa* in guinea pigs. We found a potential drug.**

Lee, Attila, Cirillo S, Cirillo J, and Wood, *Microbial Biotechnology* (2009)

Problem of Indole and 7-HI: Degradation

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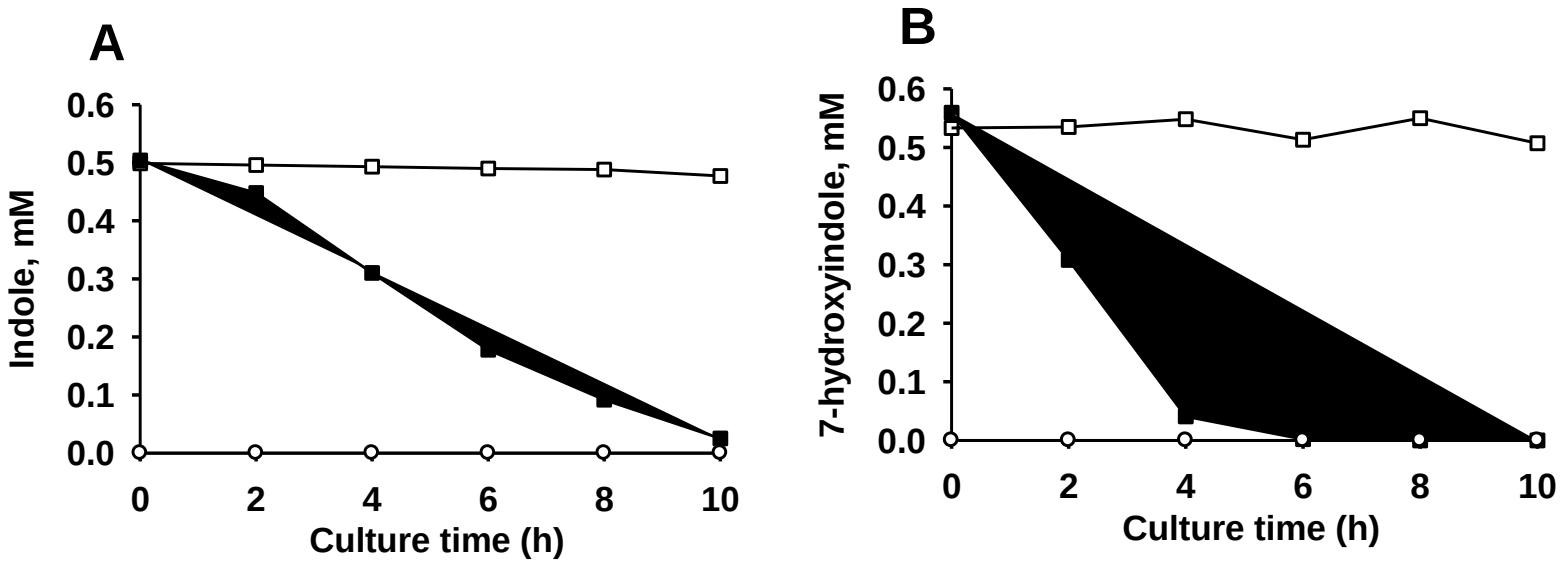
Yeungnam University

Spear and shield



Degradation of indole (A) and 7HI (B) in LB at 37°C. Closed square data (■) are from live cells.

Result: As a defense, *P. aeruginosa* degrades indole and 7-HI.

Natural Indole Derivatives

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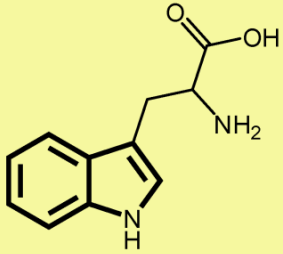
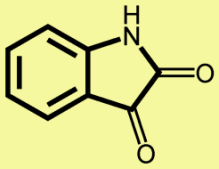
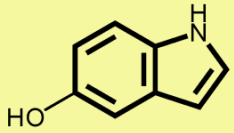
Yeungnam University

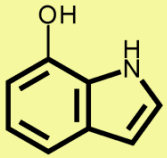
Indole motifs are in bold.

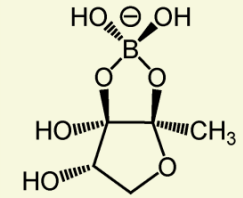
Indole

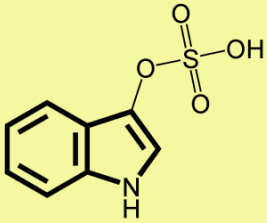

Tryptophan

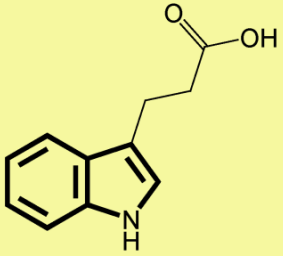

Isatin

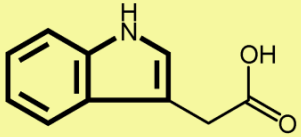

5-Hydroxyindole

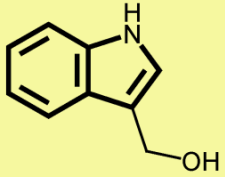

7-Hydroxyindole

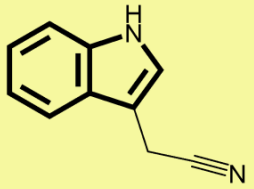

AI-2 (*V. harveyi*)

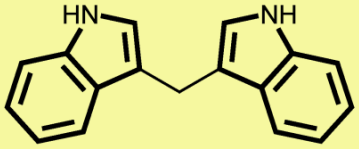

Indoxyl sulfate

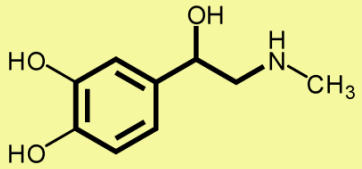

Indole-3-propionic acid

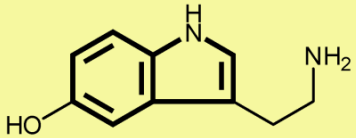

Indole-3-acetic acid

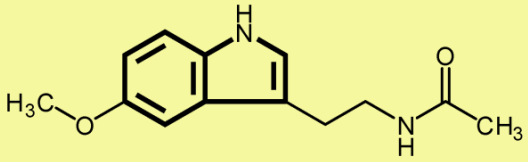

Indole-3-carbinol


3-Indolylacetonitrile


3,3'-Diindolylmethane


Epinephrine


Serotonin


Melatonin

Broccoli Contains Biofilm Inhibitors

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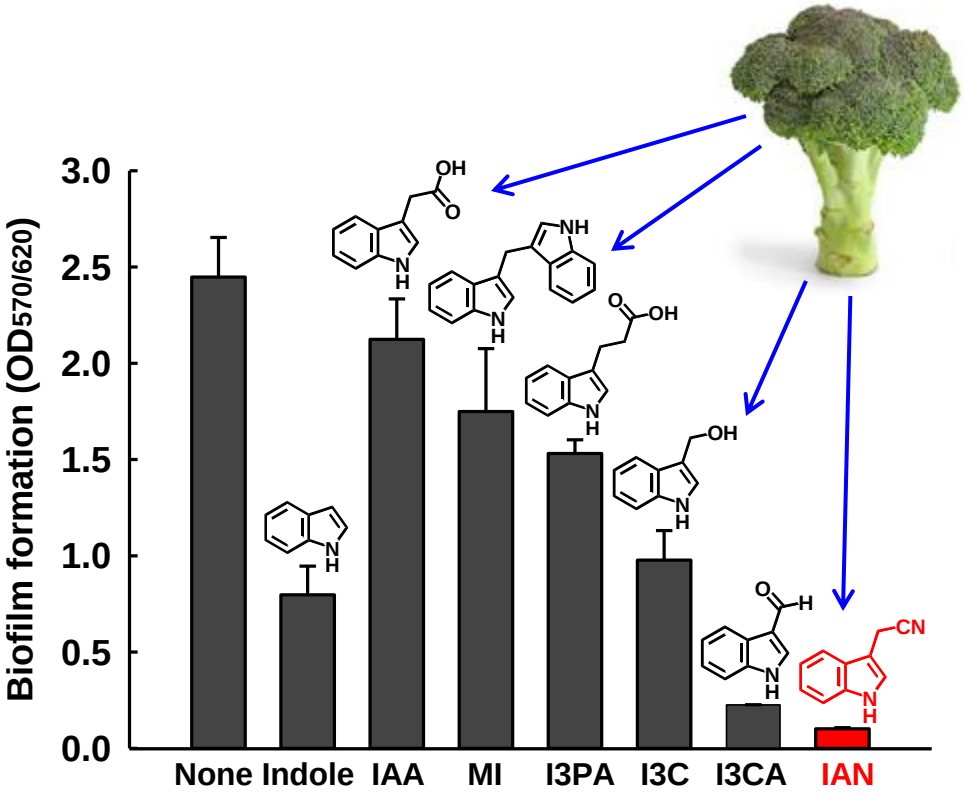
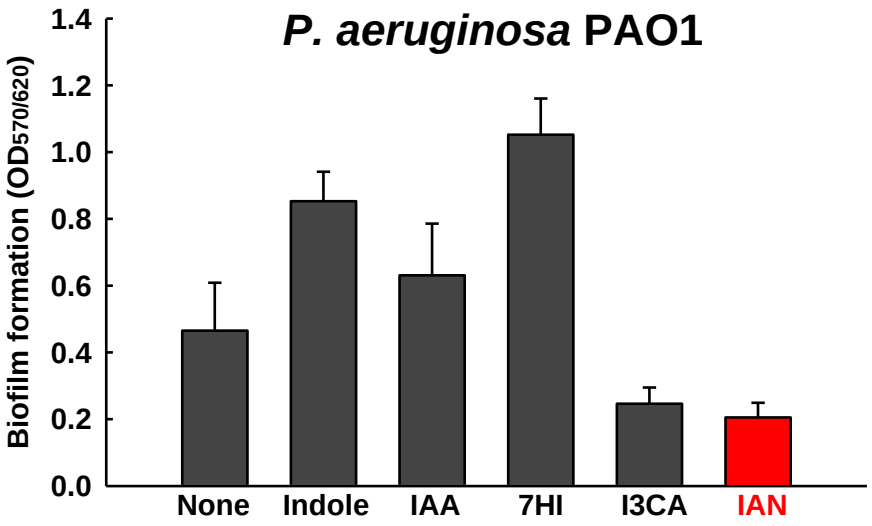
Yeungnam University





Biofilm formation of *E. coli* O157:H7.
No growth inhibition.
IAN is a plant auxin, like IAA.

Biofilm formation of *P. aeruginosa.*
No growth inhibition.

Mechanism of IAN: Polymeric Matrix (Curli)

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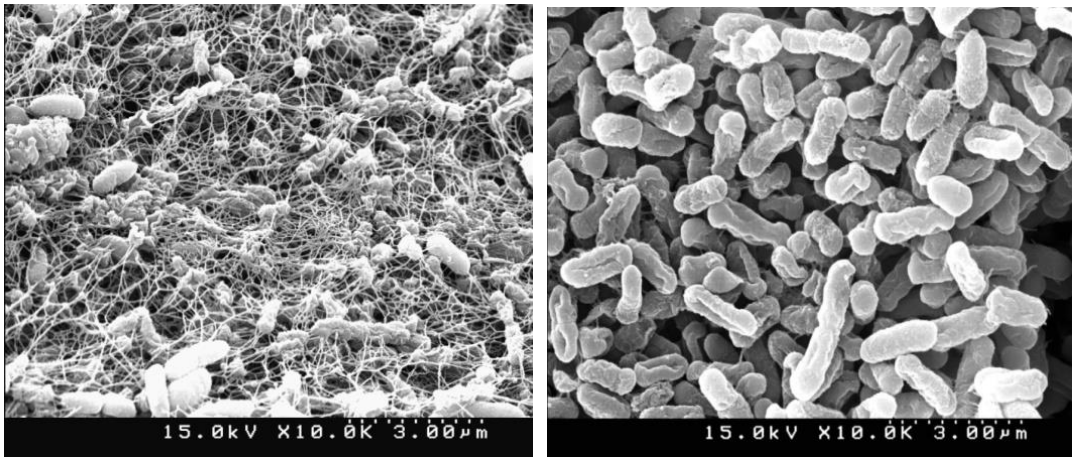
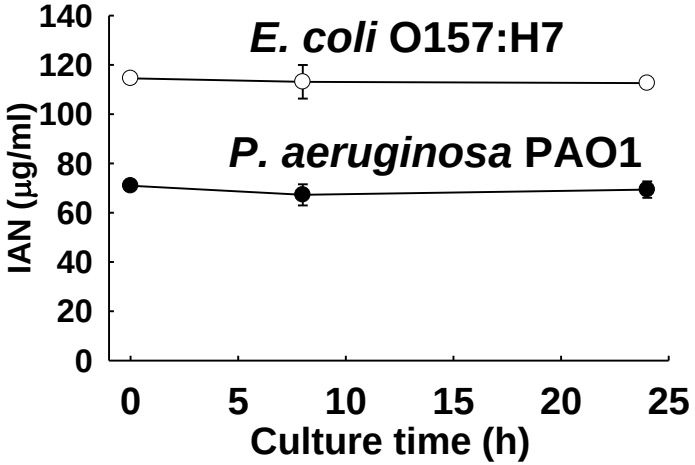
No tie → weak group

E. coli O157:H7



None IAN



Found a stable and non-toxic biofilm inhibitor against *E. coli* O157:H7

Lee, Cho, and J. Lee, *Environmental Microbiology* (2011)

Indoles Affect *Staphylococcus aureus* Virulence (Golden Cartenoid Staphyloxanthin)

영남대학교
Yeungnam University

A Cholesterol Biosynthesis Inhibitor Blocks *Staphylococcus aureus* Virulence

Chia-I Liu,[1,2,3]* George Y. Liu,[4]* Yongcheng Song,[5]* Fenglin Yin,[6] Mary E. Hensler,[7] Wen-Yih Jeng,[1,2] Victor Nizet,[7,8]† Andrew H.-J. Wang,[1,2,3]† Eric Oldfield[5,6]†

Staphylococcus aureus produces hospital- and community-acquired infections, with methicillin-resistant *S. aureus* posing a serious public health threat. The golden carotenoid pigment of *S. aureus*, staphyloxanthin, promotes resistance to reactive oxygen species and host neutrophil-based killing, and early enzymatic steps in staphyloxanthin production resemble those for cholesterol biosynthesis. We determined the crystal structures of *S. aureus* dehydrosqualene synthase (CrtM) at 1.58 angstrom resolution, finding structural similarity to human squalene synthase (SQS). We screened nine SQS inhibitors and determined the structures of three, bound to CrtM. One, previously tested for cholesterol-lowering activity in humans, blocked staphyloxanthin biosynthesis in vitro (median inhibitory concentration ~100 nM), resulting in colorless bacteria with increased susceptibility to killing by human blood and to innate immune clearance in a mouse infection model. This finding represents proof of principle for a virulence factor–based therapy against *S. aureus*.

Over the past 20 years, there has been an explosion in the prevalence of antibiotic-resistant bacterial infections, both in the hospital and in the general community; in the United States, more deaths are now attributable to methicillin-resistant *Staphylococcus aureus* (MRSA)

Unfortuna
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[1]Institute of
Taipei 1152
Throughput
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College of
10098, Taiw
Immunobiol
Center, Los
Chemistry,
[6]Center for
of Illinois, Ur
University of
[8]Skaggs Sch
University of

*These auth
†To whom c
vnizet@ucs
(A.H.-J.W.);

www.sciencemag.org SCIENCE VOL 319 7 MARCH 2008

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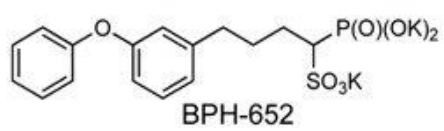
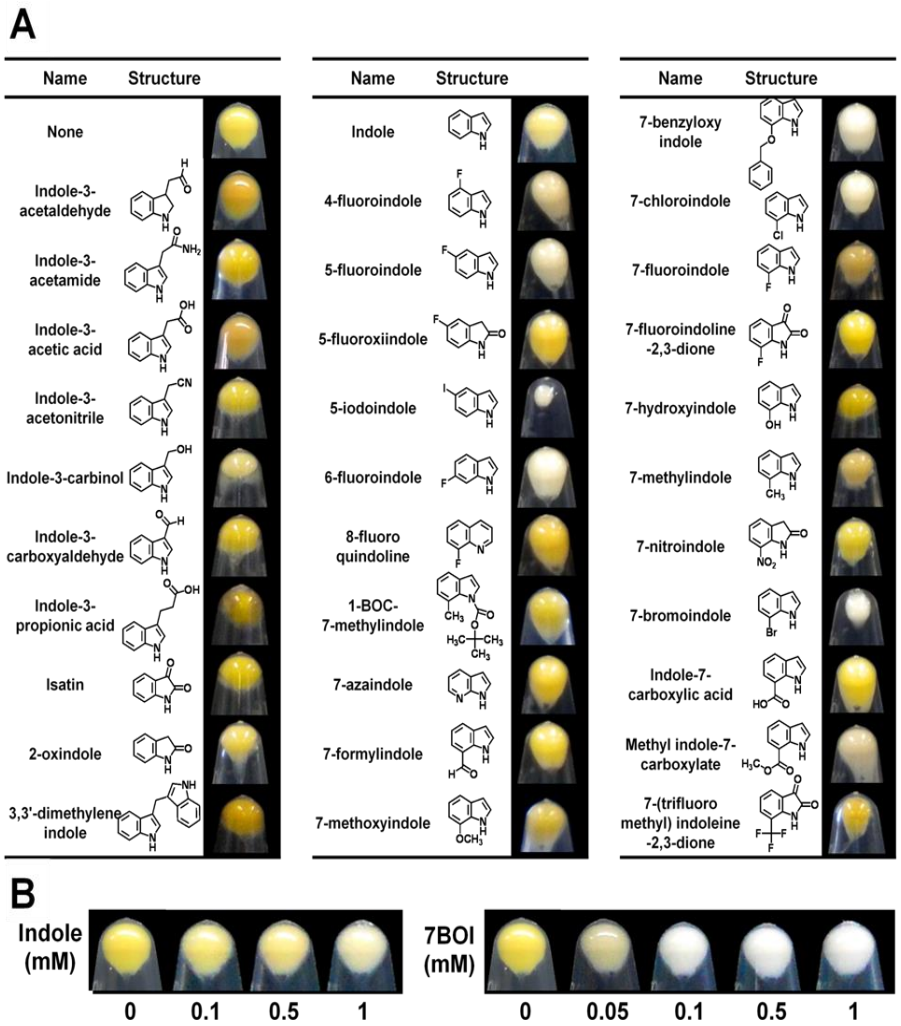


BPH-652

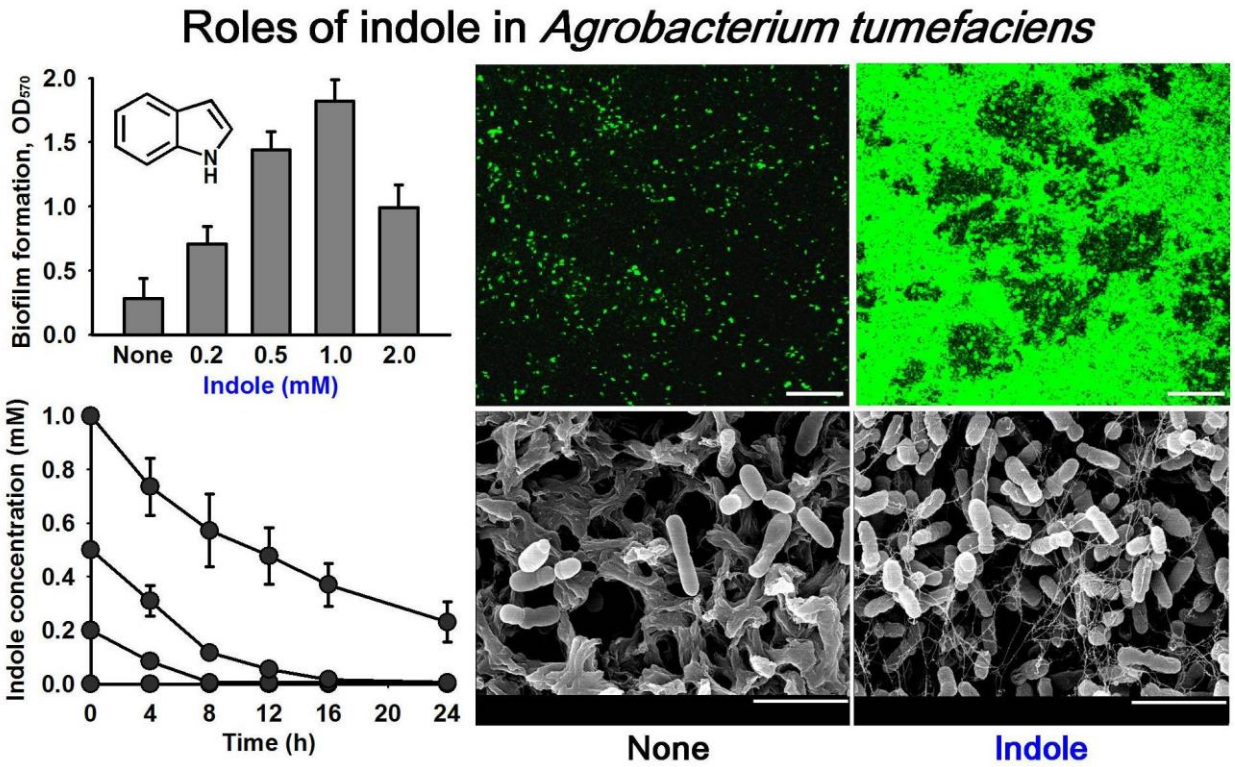


Lee, Cho, Kim, Kim, Banskota, Cho, and J. Lee, *Applied Microbiology and Biotechnology* (2013)

Indole Increases Biofilm Formation of *Agrobacterium tumefaciens*

영남대학교
Yeungnam University

***A. tumefaciens* is a plant pathogen causing crown gall**



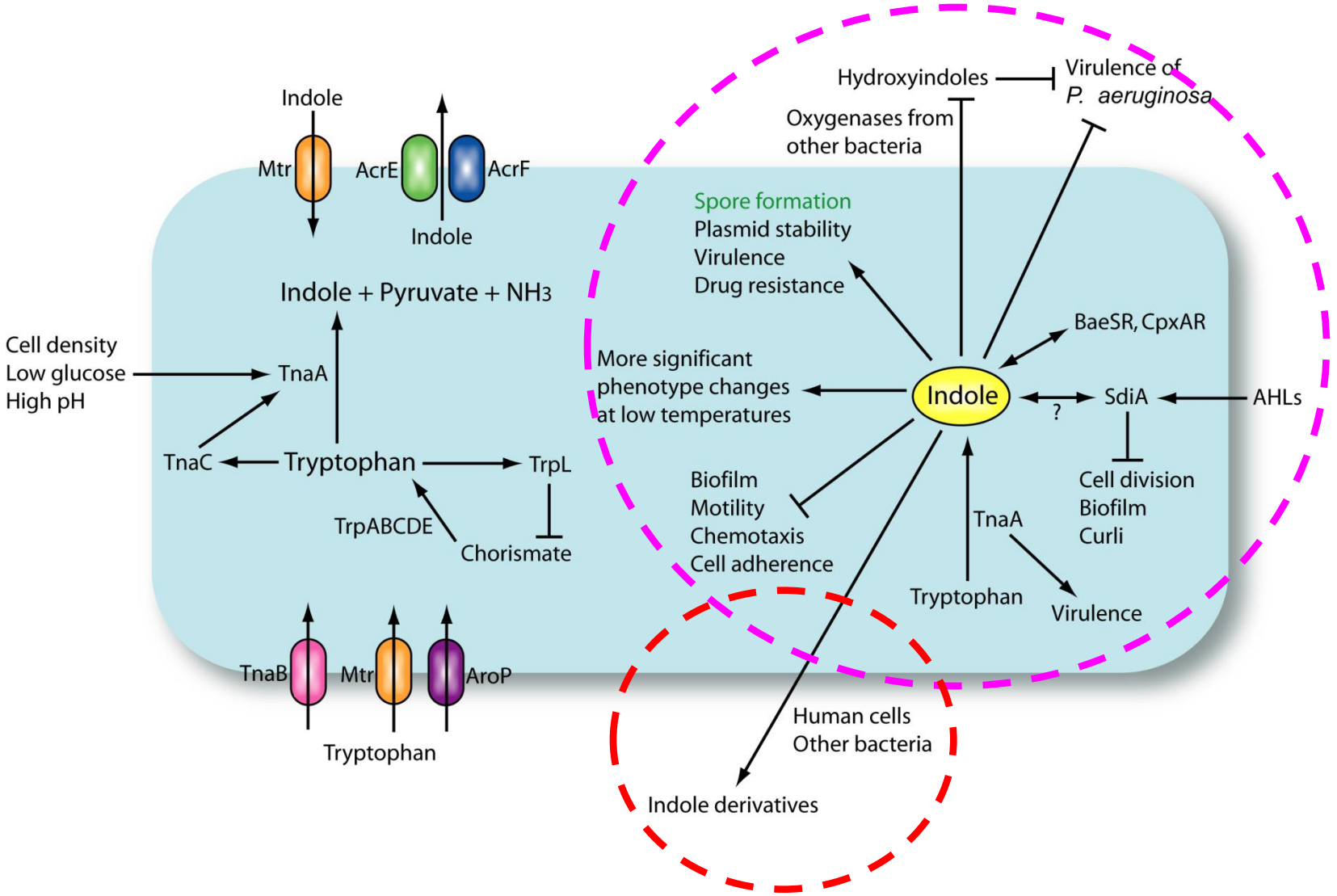
Lee, Kim, Baek, Cho, and J. Lee, *Environmental Microbiology* (2015)

Effect of Indoles on Other Bacteria

영남대학교 Yeungnam University

Bacteria	Indole compound	Phenotypic change	Mechanism	Ref
Acinetobacter baumannii	Indole derived flus tramine,	Inhibition of biofilm formation	Unknown	[46]
Acinetobacter oleivorans	Indole	Inhibition of biofilm formation and motility	Inhibition of QS regul ator folding	[54]
Bdellovibrio bacteriovorus	Indole	Reduction of predation	Downregulation of fla gellar and ribosome a ssembly genes	[60]
Burkholderia unamae	Indole and gallic a cid	Induction of biofilm formation	Unknown	[59]
Candida albicans	Indole and 3-indolylacetonitril e	Reduction of biofilm formation and virulence	Stimulation of transcr iptional factor	[56]
Chromobacterium violaceum *Pseudomonas chlororaphis* *Serratia marcescens*	Indole	Inhibition of QS- regulated pig mentation	QS inhibition	[55]
Cylindrotheca sp.	Indole and its derivatives	Inhibition of growth and biofil m formation	Induction of cellular Ca^{2+} efflux	[66]
Salmonella enterica serovar Typhimurium	Indole	Increase of antibiotic tolerance	Oxidative stress respo nse	[61]
Salmonella enterica serovar Typhimurium	Indole	Increase of antibiotic tolerance and decrease of motility	Activation of efflux p ump and suppression of flagellar genes	[62,63]

Indole in Microbial Community



J-H. Lee and J. Lee, *FEMS Microbiology Reviews* (2010, >220 citations)

Functions of Indole in Plants?

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nature COMMUNICATIONS

ARTICLE

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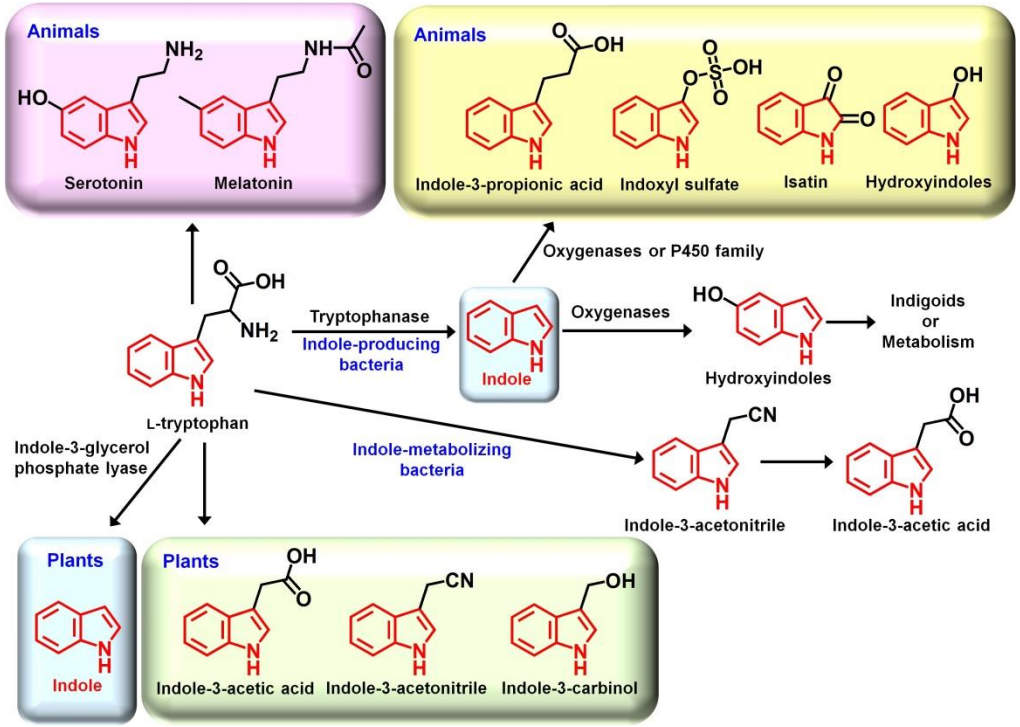
DOI: 10.1038/ncomms7273 OPEN

Indole is an essential herbivore-induced volatile priming signal in maize

Matthias Erb[1,*], Nathalie Veyrat[2,*], Christelle A.M. Robert[1], Hao Xu[2], Monika Frey[3], Jurriaan Ton[4] & Ted C.J. Turlings[2]



Indoles on plants?

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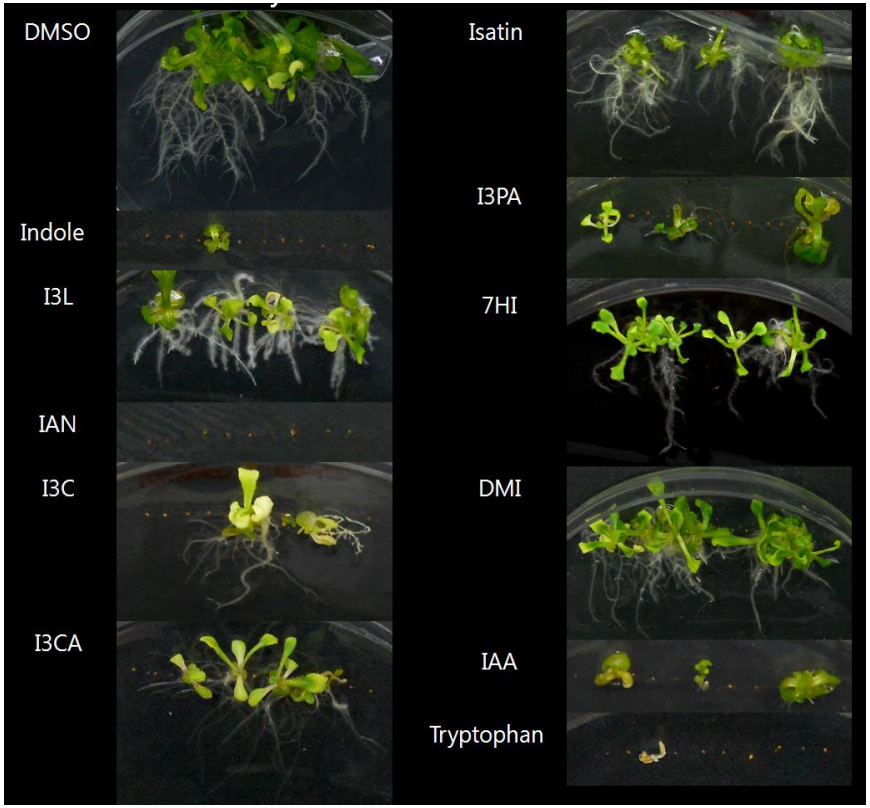
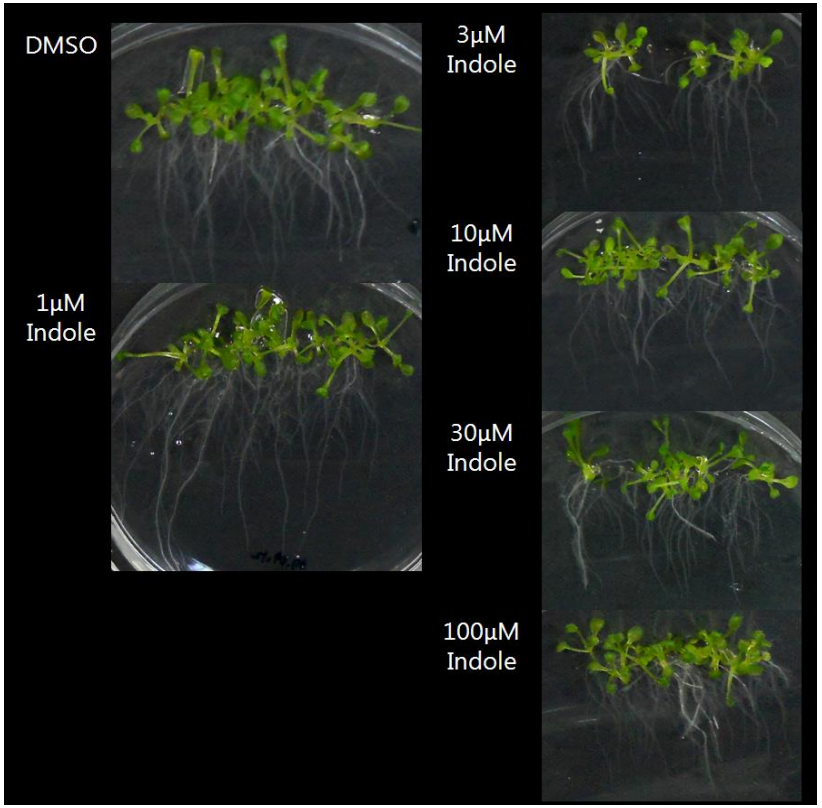
Yeungnam University

Hypothesis: volatile indoles enhance plant growth and immunity.

Arabidopsis thaliana



High concentration of indoles at 0.5 mM



Low concentration of indole

(Unpublished)

Functions of Indole in Animals?

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Yeungnam University

Germ-free mouse
(no indole in gut)

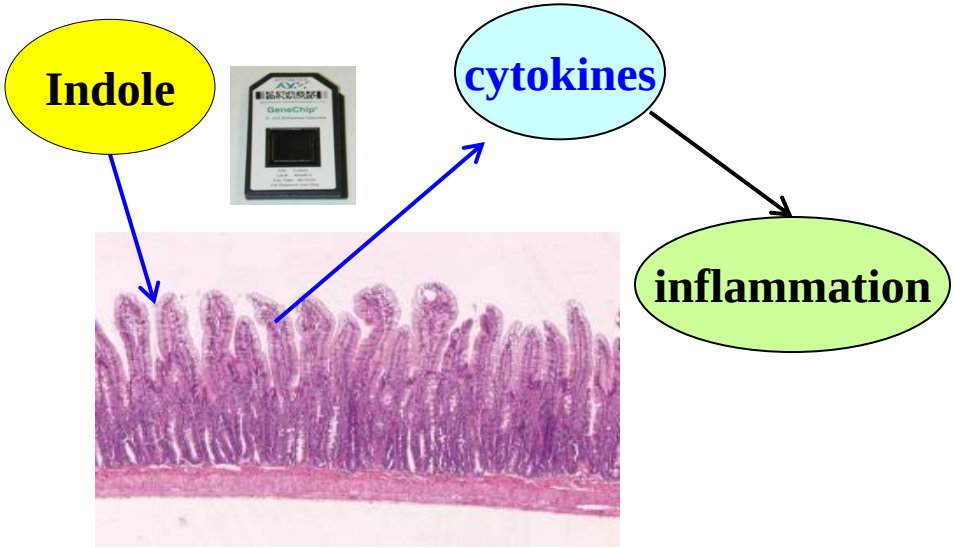
regular mouse
(indole in gut)

metabolomics

no indole-3-propionic acid in blood

indole-3-propionic acid in blood

- Indole-3-propionic acid
  = a powerful antioxidant
  (Wikoff *et al.*, 2009, *PNAS*)



Human Intestinal Epithelial Cell

- (Wood *et al.*, 2010, *PNAS*)

Functions of Indole in Human?

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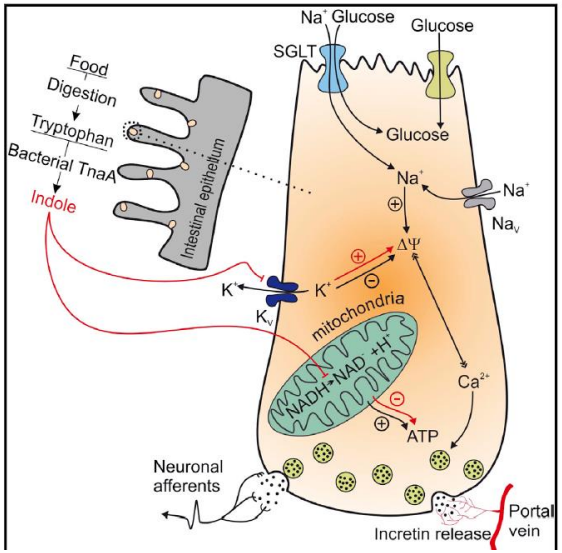
Yeungnam University

Cell Reports

Bacterial Metabolite Indole Modulates Incretin Secretion from Intestinal Enteroendocrine L Cells

Graphical Abstract



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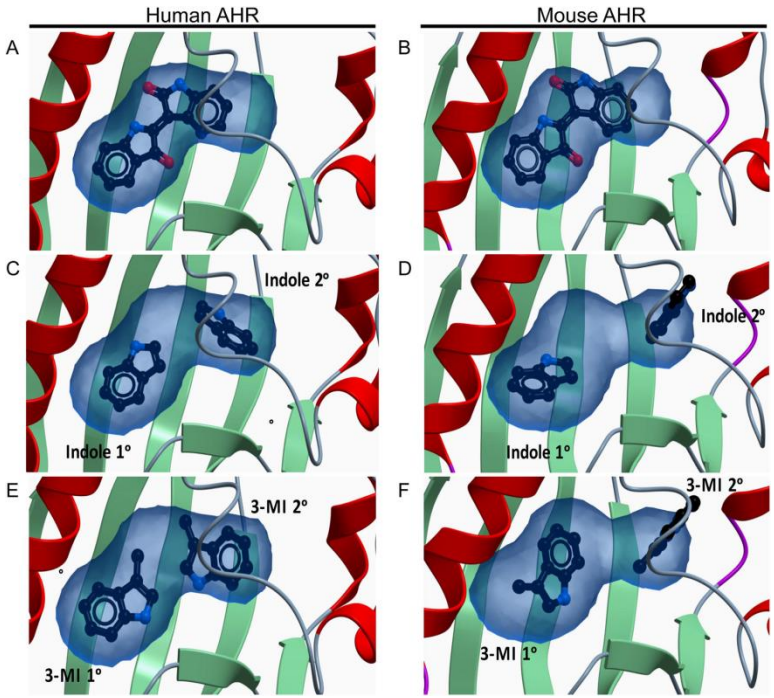
In Brief

Indole is the main metabolite produced by gut bacteria from tryptophan. Chimerel et al. demonstrate that indole modulates the hormone secretion of enteroendocrine L cells and reveal the molecular mechanism behind this modulation. These findings suggest that the production of indole by bacteria could have a major impact on host metabolism.



SCIENTIFIC REPORTS

OPEN

Adaptation of the human aryl hydrocarbon receptor to sense microbiota-derived indoles

Received: 19 March 2015
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Troy D. Hubbard[1,2], Iain A. Murray[2], William H. Bisson[3], Tejas S. Lahoti[2], Krishne Gowda[4], Shantu G. Amin[4], Andrew D. Patterson[2] & Gary H. Perdew[2]

Indole in Bacteria, Plants, and Insects, and Animals as a Signaling Molecule

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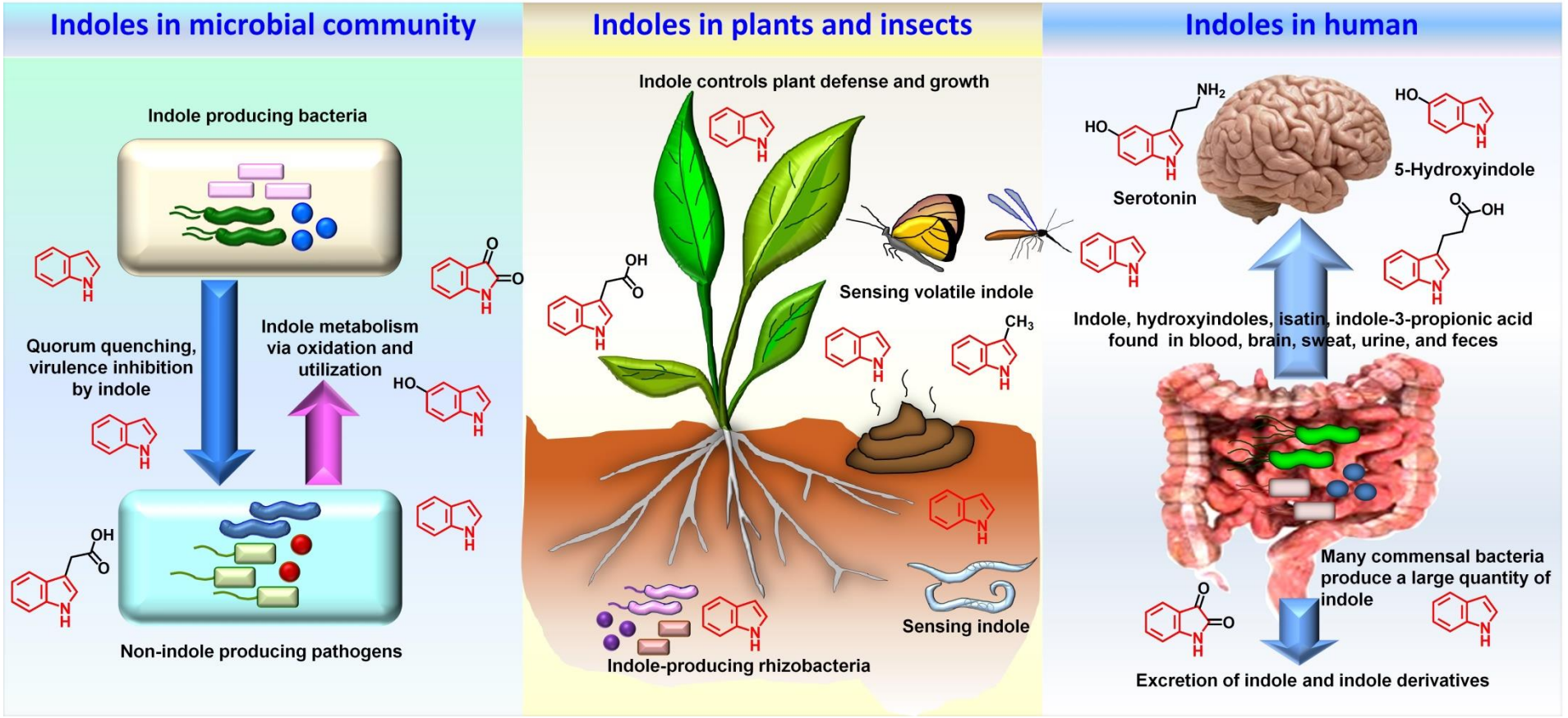

J-H Lee, TK Wood, and J Lee, *Trends in Microbiology* (2015)

Indoles in *Caenorhabditis elegans*

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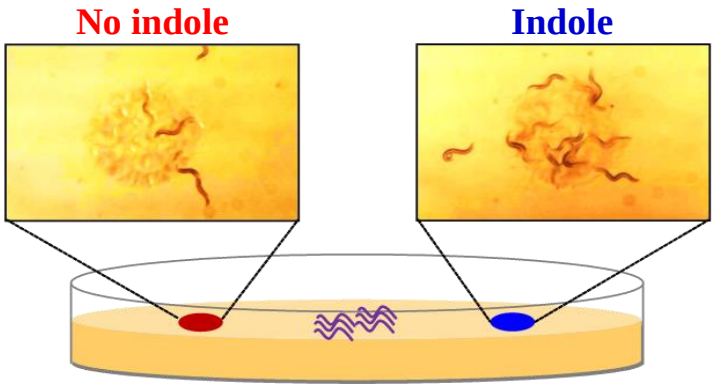

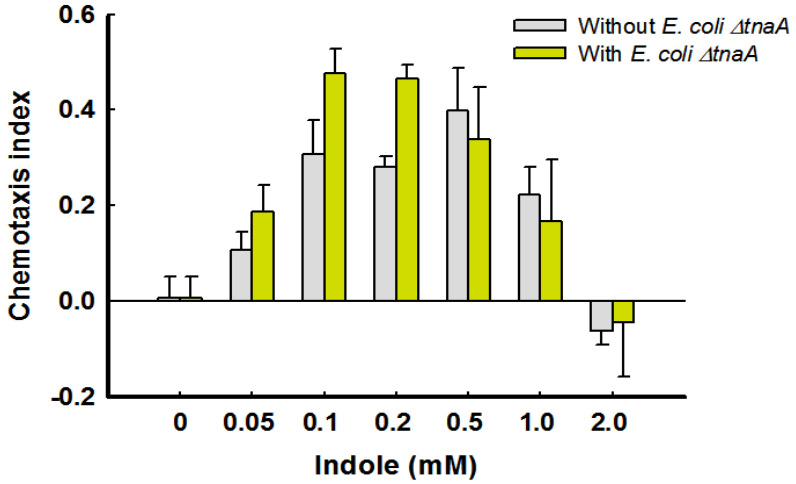

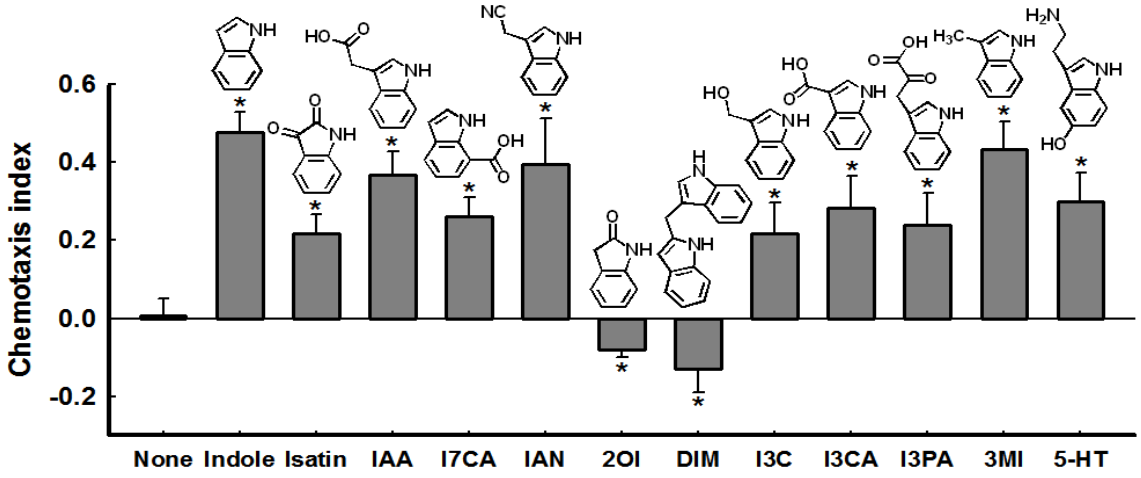

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- *C. elegans* senses indole and its derivatives

Indole degradation by *C. elegans*

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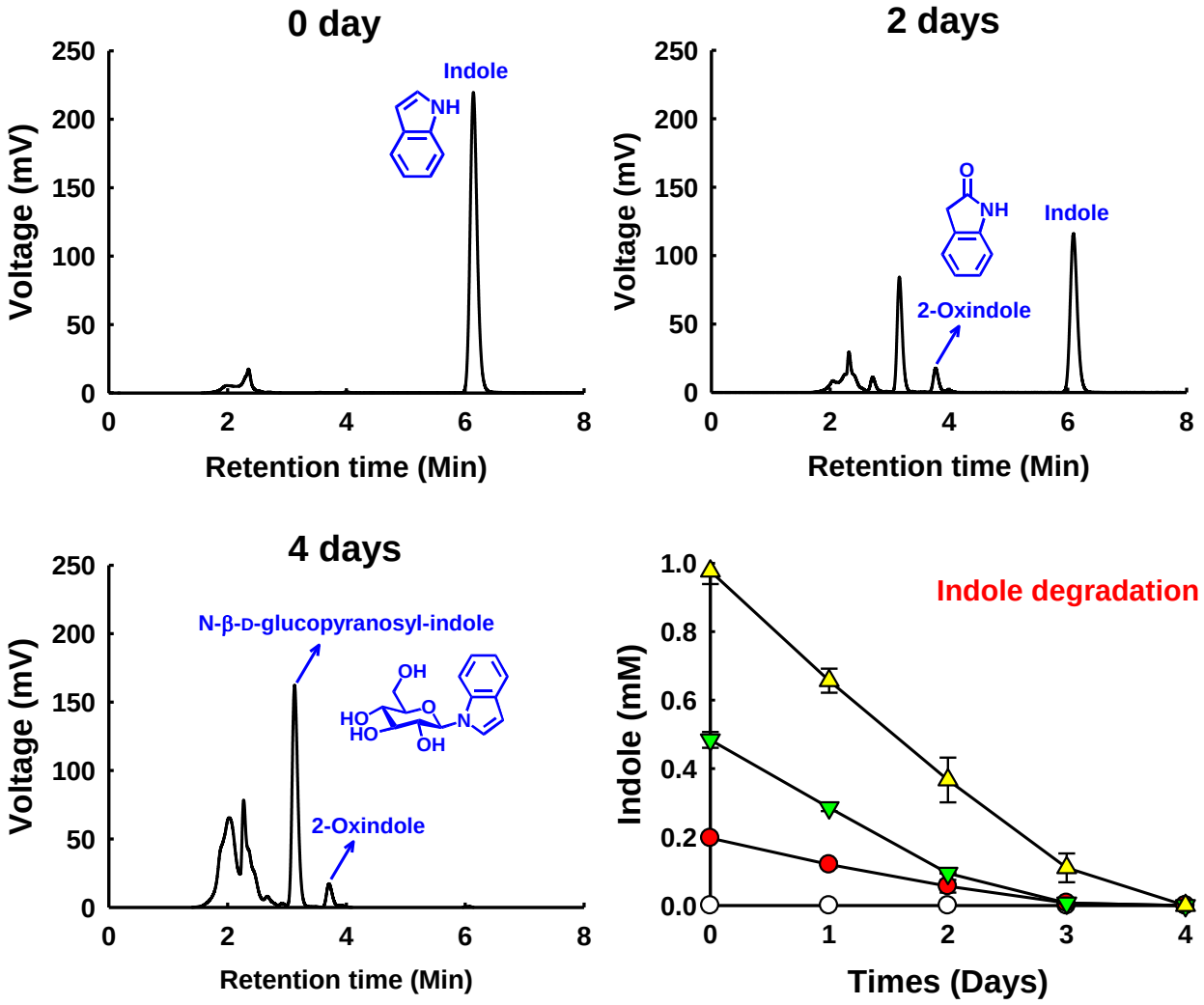

- *C. elegans* degrades indole by oxidation of glycosylation.

Indole controls gene expression of *C. elegans*

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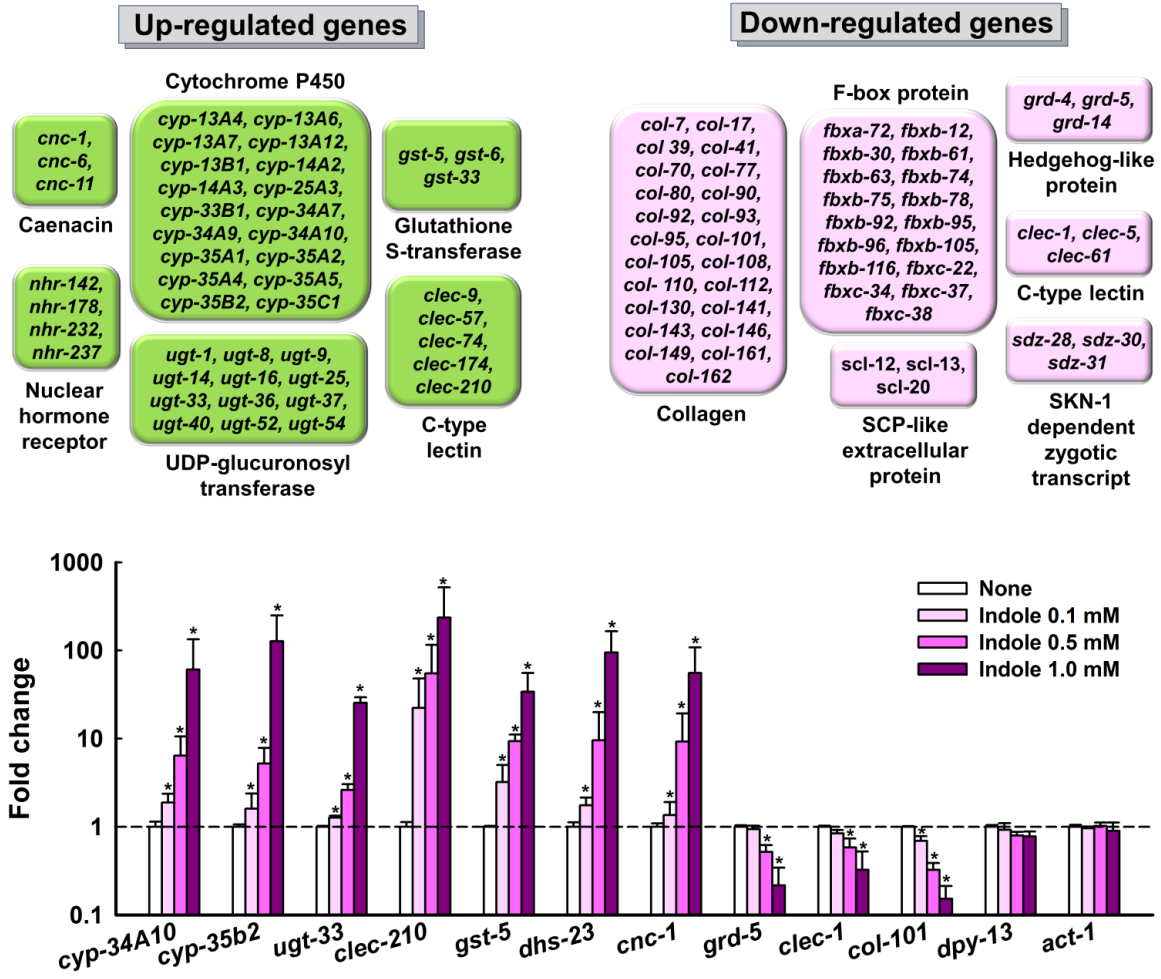

- **Indole control expression of many genes in *C. elegans*.**

Model of bacteria-nematode interactions

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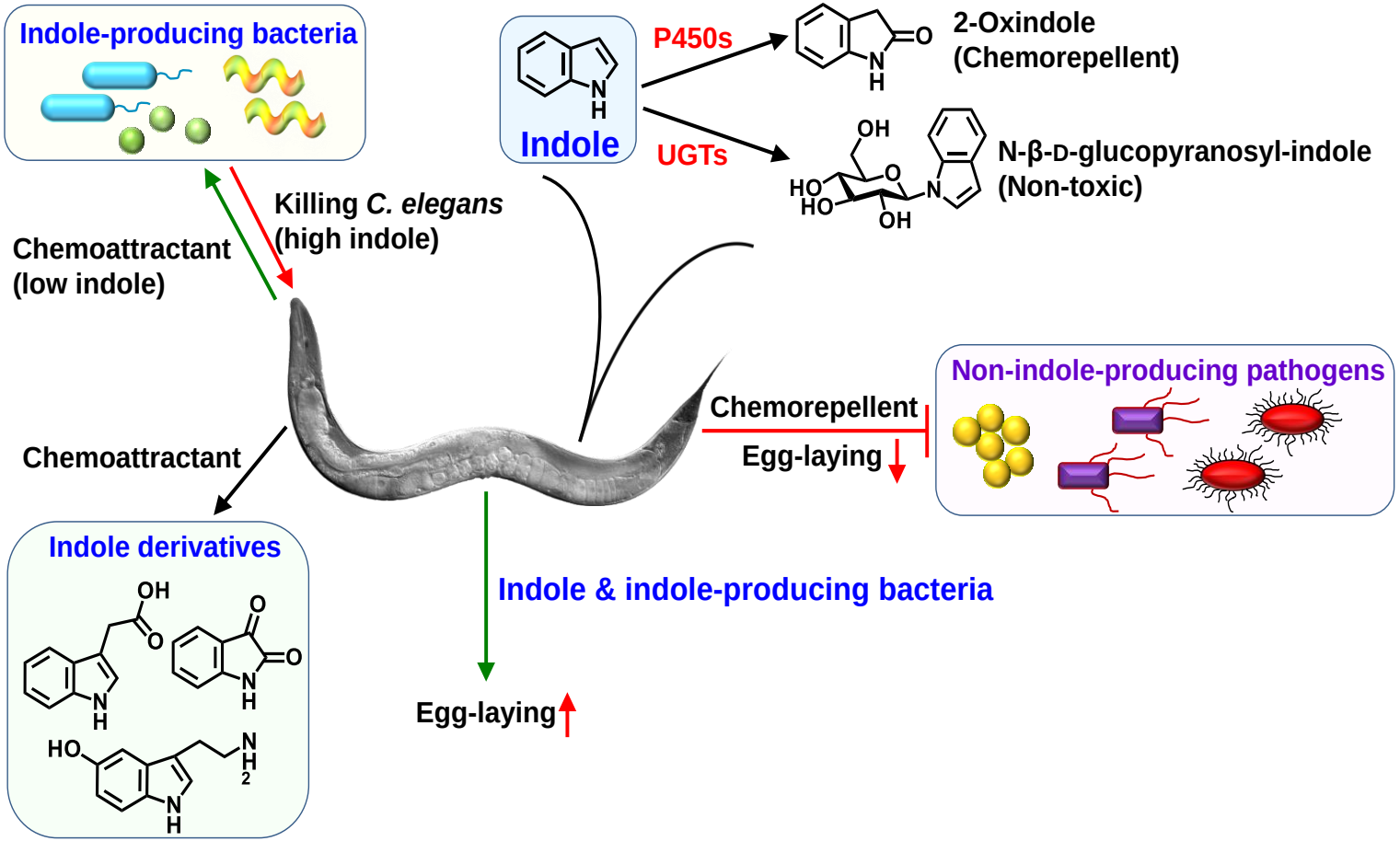

Environmental Microbiology (2017 online)

Killing pine tree nematode with indoles

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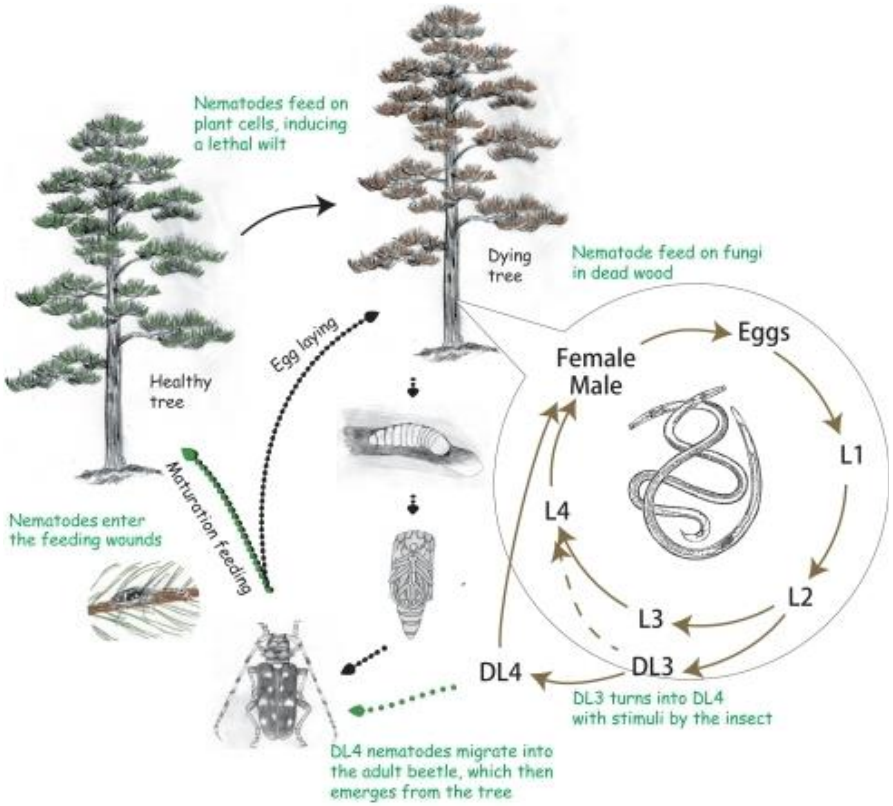

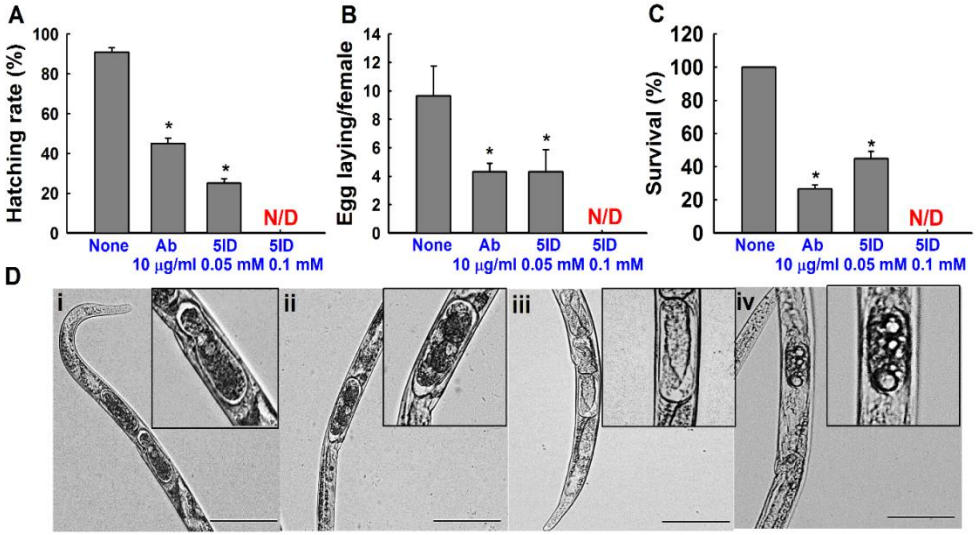

Some indole (like Abamectin) can kill pine tree nematode.

Indoles produce vacuoles and non-toxic to plants

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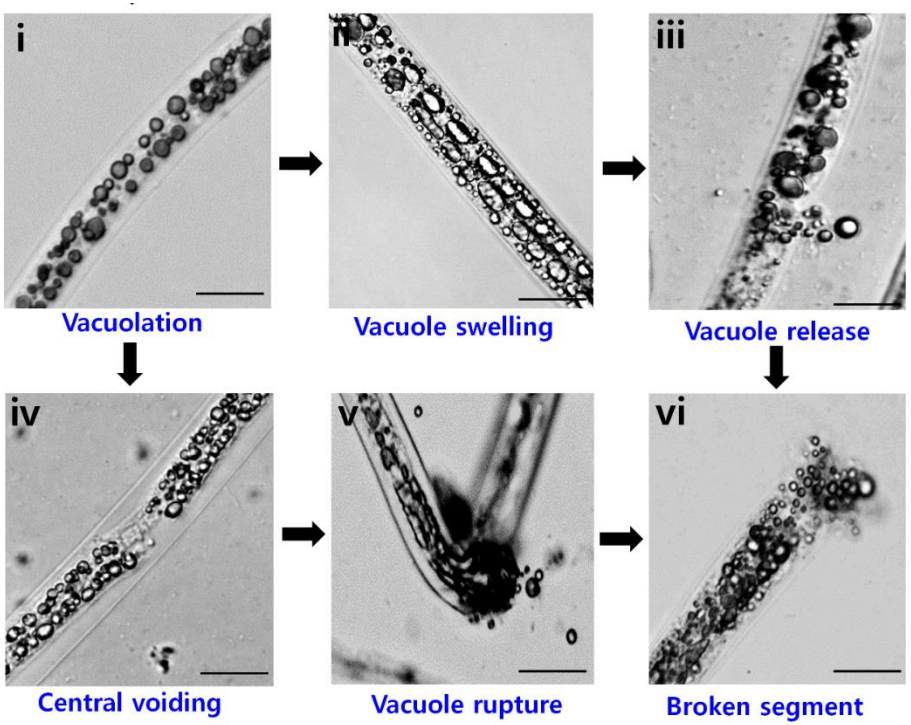

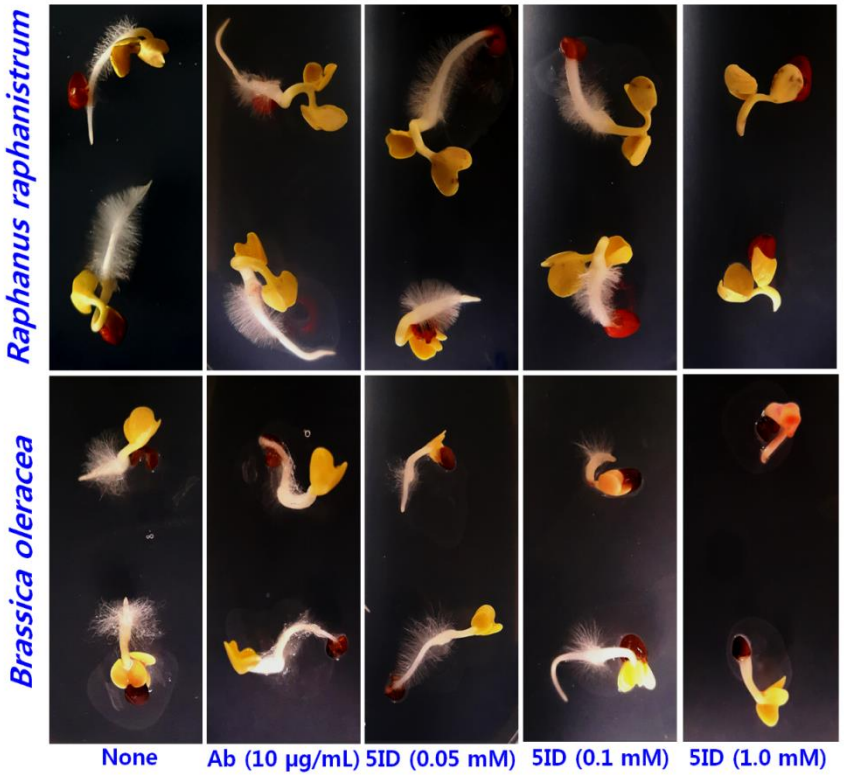

Some indoles are new nematicides

(under review)

Conclusion of indole story

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Indole and its derivatives are intercellular, inter-species, and inter-kingdom signaling molecules.

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- **Ph.D. student: YG Kim**
- **M.S. students: MS Kim, GY Kwon**

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