Critical Reviews in Microbiology

ISSN: 1040-841X (Print) 1549-7828 (Online) Journal homepage: https://www.tandfonline.com/loi/imby20

Quenching the quorum sensing system: potential antibacterial drug targets

Vipin Chandra Kalia & Hemant J. Purohit

To cite this article: Vipin Chandra Kalia & Hemant J. Purohit (2011) Quenching the quorum sensing system: potential antibacterial drug targets, Critical Reviews in Microbiology, 37:2, 121-140, DOI: 10.3109/1040841X.2010.532479

To link to this article: https://doi.org/10.3109/1040841X.2010.532479

Published online: 27 Jan 2011.

Critical Reviews in Microbiology, 2011; 37(2): 121–140

ISSN 1040-841X print/ISSN 1549-7828 online
DOI: 10.3109/1040841X.2010.532479

informa
healthcare

REVIEW ARTICLE

Quenching the quorum sensing system: potential antibacterial drug targets

Vipin Chandra Kalia[1], and Hemant J. Purohit[2]

[1]Microbial Biotechnology and Genomics, Institute of Genomics and Integrative Biology (IGIB), CSIR, Delhi University Campus, Mall Road, Delhi-110007, India, and [2]Environmental Genomics Unit, National Environmental Engineering Research Institute (NEERI), CSIR, Nehru Marg, Nagpur - 440020, India

Abstract

Emergence of antibiotic and multi-drug resistant pathogenic bacteria has created the need for new drugs and drug targets. During pathogenesis bacteria release signals which regulate virulence and pathogenicity related genes. Such bacteria co-ordinate their virulent behaviour in a cell density dependent phenomenon termed as quorum sensing (QS). In contrast, microbes interfere with QS system by quenching the signals, termed quorum quenching (QQ). As a consequence of disrupted QS, pathogens become susceptible to antibiotics and drugs. In this article, the biodiversity of organisms with potential to quench QS signals and the use of QQ molecules as antibacterial drugs have been reviewed.

Keywords: Antibiotics, Bacillus, enzymes, pathogens, signal, virulence

Introduction

In the present era, one of the primary concerns in public health is the emergence and proliferation of multi-drug resistant microbial strains (Cars et al. 2008). The magnitude of the problem is enhanced by the rapid genetic changes in microbes which confer resistance even to the most recently developed drugs (Wright 2005; Marris 2006; Sundaramurthy & Pieters 2007; Courvalin 2008). This scenario has forced researchers to look for novel microbes for producing antibiotics (Kalia et al. 2007) or alternatives to manipulate the virulence genes in pathogens, which get expressed through bacterial co-ordination (Rasmussen & Givskov 2006a). Bacteria ensure appropriate and robust coordination by communicating through signal molecules (Chen et al. 2005; Dunny et al. 2008; von Bodman et al. 2008), which are released in a cell-density dependent manner, termed as quorum sensing (QS) (Winzer et al. 2002) (Figure 1). QS is a true cell-to-cell communication behaviour widely observed among prokaryotes (Zhu et al. 2002) not only for interacting among those living in their close proximity (Flannery 2006) but also for making collective decisions (von Bodman et al. 2008). It leads to the expression and regulation of processes which extend beyond the normal cellular responses such as i) bioluminescence, ii) biofilm formation, iii) regulation of virulence genes, iv) antibiotic production, v) nitrogen fixation, vi) conjugal transfer of plasmid DNA, vii) swarming, viii) biocorrosion, ix) spore formation, x) competence, x) fruiting body formation, and so on (Baca-DeLancey et al. 1999; Winans & Bassler 2002; Wisniewski-Dyé & Downie 2002; Zhu et al. 2002; Wright et al. 2004; Waters & Bassler 2005; Chevrot et al. 2006; Dunny et al. 2008; Defoirdt et al. 2010). These biological activities ensure better survival in natural environments, where microbes within a community compete for scarce resources (Chen et al. 2005; Hibbing et al. 2009). In response to these specific survival mechanisms, quite a few bacteria produce bioactive molecules to disturb the QS system by a process termed as quorum quenching (QQ). It primarily attenuates the expression of virulent behaviour in pathogenic bacteria (Chen et al. 2009) without restricting their growth (Manefield et al. 2000; Defoirdt et al. 2006). In the absence of any harsh selective

Address for Correspondence: Kalia, V.C., Microbial Biotechnology and Genomics, Institute of Genomics and Integrative Biology (IGIB), CSIR, Delhi University Campus, Mall Road, Delhi-110007, India. E-mail: vckalia@igib.res.in

(Received 11 February 2010; revised 01 September 2010; accepted 13 October 2010)

Abbreviations

AHL, Acylhomoserine lactone
HSL, Homoserine lactone
C4HSL, N-butanoyl-L-HSL
C6HSL, N-hexanoyl HSL
C7HSL, N-heptanoyl-HL
C8HSL, N-octanoyl HSL
C10HSL, N-decanoyl HSL
C12HSL, N-dodecanoyl HSL
C14HSL, N-tetradecanoyl-HSL
C16HSL, N-hexadecanoyl-HSL
3OC6HSL, 3-oxo-N-hexanoyl-HSL
3OC8HSL, 3-oxo-N-octanoyl-HSL
3OC10HSL, 3-oxo-N-decanoyl-HSL
3OC12HSL, 3-oxo-N-dodecanoyl-HSL
3OC14HSL, 3-oxo-N-tetradecanoyl-HSL
OHC4HSL, 3-hydroxy-N-butanoyl-HSL
OHC10HSL, 3-hydroxy-N-decanoyl-HSL
OHC14HSL, 3-hydroxy-N-tetradecanoyl-HSL

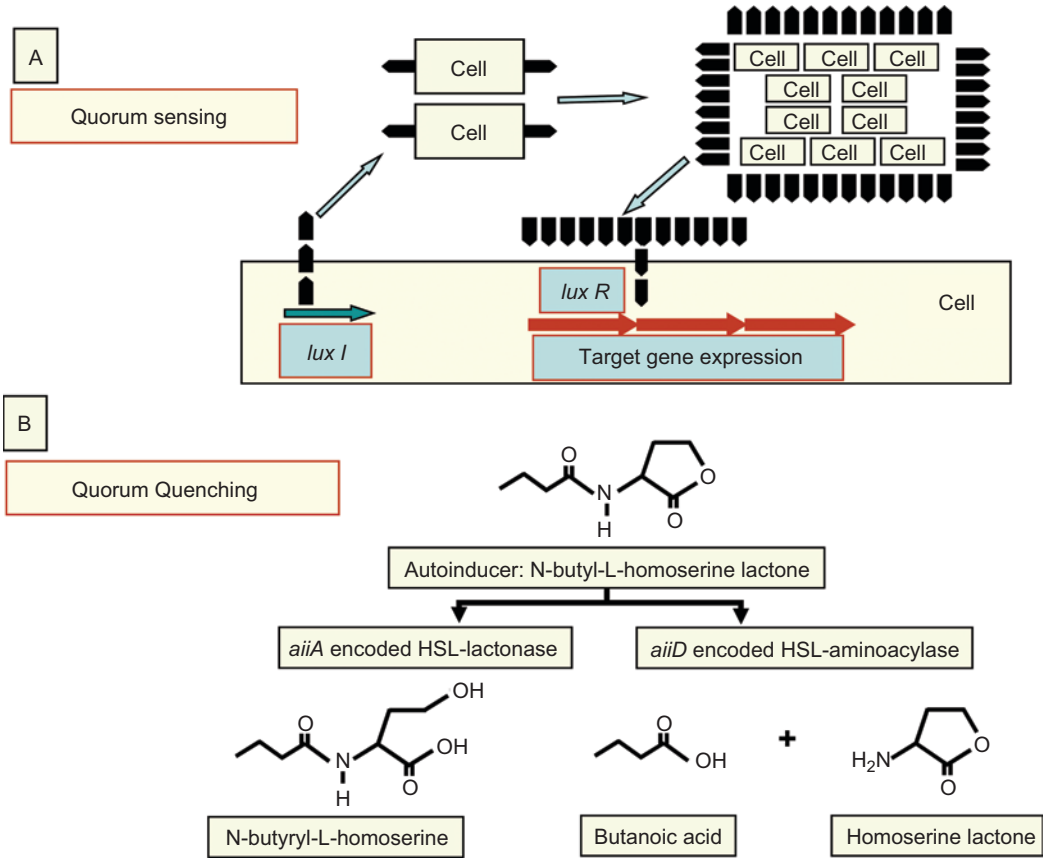

Figure 1. A: Quorum sensing. QS initiates with the activation of *lux*I leading to the production of signal molecules (➡, filled arrow) (acyl-homoserine lactones, acyl-HSL), which are released into the environment. At high cell densities, these signal molecules are retrieved into the cell resulting in the expression of target genes (virulence, etc.) through *luxR*. B: Quorum quenching. QQ is initiated by the inactivation of quorum sensing signal (acyl-HSL) by enzymes—lactonase (Hydrolysis of lactone ring) and acylase (Cleavage of the acyl side chain) generally produced by gram-positive (*Bacillus* sp.) and gram-negative bacteria (*Ralstonia* sp.) respectively.

pressure being imposed on bacteria, the pressure to develop resistance to antibiotics is negligible (Rasmussen & Givskov 2006b; Defoirdt et al. 2008). The excitement on the possibilities of interference with microbial communication to prevent expression and dissemination of virulence factors among pathogens has lead to the emergence of an interesting and innovative system for searching novel drug targets and drug designing (Chowdhary et al. 2007; Dobretsov et al. 2007; Opal 2007; Purohit et al. 2007; Turovskiy et al. 2007; Uroz et al. 2007, 2008; Uroz & Heinon 2008; Adonizio et al. 2008; Romero et al. 2008; Schaefer et al. 2008; von Bodman et al. 2008). In this article, we are attempting to present the diversity of the potential organisms and the mechanisms, which can be exploited for developing antibacterial drugs through QQ (Czajkowski & Jafra 2009).

Quorum sensing systems

Pathogenic microbes have been bestowed with a unique ability to grow and multiply without displaying their virulent behaviour until they have reached a certain threshold of cell population density (Figure 1). At this stage, they release signals which activate their arsenal of virulence genes and a cascade of activities follows there after (Wagner et al. 2006; Bjarnsholt & Givskov 2008). QS allows bacteria to change their behavior from individual activity to a collective coordinated expression and act like

a "multicellular" organism (Schauder & Bassler 2001). Multiplicity of QS systems, signals, and the differences in their operational level and activities provide bacteria with a resilient and adaptable signaling network (Decho et al. 2010). It may enable bacteria to do a quick survey of their surrounding and develop a strategy to counter the threats (Yang et al. 2006). The following few examples provide a glimpse of the diversity of bacterial behaviours manifested through QS.

Bioluminescence

The emission of light observed in a symbiotic association between marine bacterium—*Photobacterium fischeri* (Formerly known as *Vibrio fischeri*) and its host, the squid— *Euprymna scolopes* is among the first few examples found to be regulated by QS. Here *P. fischeri* obtains its nutrients from the host, which in exchange uses the light produced by *P. fischeri* at high cell density for attracting prey, avoiding predators or finding its mating partner (Nealson et al. 1970; Schauder & Bassler 2001).

Biofilms and infections

QS systems, which are very important from medical application point of view include biofilm development and expression of virulence factors (Schertzer et al. 2009). *Pseudomonas aeruginosa,* a human opportunistic pathogen forms QS regulated biofilms in the lungs of cystic fibrosis patients. These biofilms are secondarily colonized by *Burkholderia cepacia* strains (Schauder & Bassler 2001), the only pathogen more dreadful than *P. aeruginosa*, and virtually spells "death sentence" for CF patients (Hassett et al. 2009). These matrix-enclosed structures are responsible for persistence and severity of *P. aeruginosa* (Rahme et al. 2000; Ueda & Wood 2009).

Among the Gram-positive bacteria are members of Streptococci which colonize epithelial, mucosal, and tooth surfaces (Suntharalingam & Cvitkovitch 2005). In dental plaques colonized by *Streptococcus intermedius*, *S. mutans*, *S. pneumoniae*, *S. gordonii*, and so on competence-stimulating peptide mediated QS is closely linked with biofilm formation (Petersen et al. 2004; Antunes et al. 2009). Another pathogen of concern is *Staphylococcus aureus*, which manifests skin and lung infections through QS dependent biofilms (Schauder & Bassler 2001; Yarwood & Schlievert 2003).

Antibiotic production

QS mechanism is often used by a wide range of microbes for producing antibiotics. QS signals (peptides) are used by Gram-positive microbes belonging to Firmicutes—*Streptococcus*, *Lactococcus*, and *Bacillus* to produce antibacterial peptides, Nisin and Subtilin, respectively (Kuipers et al. 1995; Stein et al. 2002; Hazan & Engelberg-Kulka 2004). Production of antibiotics violacein by *Chromobacterium violaceum* and phenazine by *Pseudomonas chlororaphis* PCL1391 are regulated by AHL mediated QS ((McClean et al. 1997; Molina et al. 2003). AHLs act as signaling molecules among proteobacteria such as *Pseudomonas* spp., *Erwinia*, *Burkholderia*, *Serratia*, and so on for regulating antibiotic production (Hibbing et al. 2009; Raina et al. 2009).

Rhizospheric activities

In plant associated bacteria such as *Rhizobium* and *Agrobacterium*, QS participates in rhizospheric specific genes, conjugal DNA transfer, symbiotic nitrogen fixation, growth, production of secondary metabolites, antifungal compounds, antibiotics, and a large number of extracellular enzymes (Somers et al. 2004). Conjugal transfer of DNA in *Agrobacterium tumefaciens,* a soil phytopathogenic bacterium to the plant host is mediated by Ti plasmid encoded *vir* (virulence) genes in response to certain phenolic compounds, which are released from the plant wounds (Luo & Farrand 1999; Zhu & Winans 1999).

Quorum sensing signals

Bacteria have evolved a number of diffusible chemical signals to control various biological activities (Newton & Fray 2004). The QS signals vary from organism to organism: i) AHLs in *Vibrio* (Fuqua et al. 1994; Fuqua & Greenberg 1998), ii) The Lux-S-derived family of furanone signals (AI-2) in *Vibrio harveyi* (Schauder & Bassler 2001; Xavier & Bassler 2003), iii) Volatile fatty acid and methyl ester signal in *Ralstonia solanacearum* (Flavier et al. 1997), iv) PQS: 2-heptyl-3-hydroxy-4-quinolone and diketopiperazines in *P. aeruginosa* (Pesci et al. 1999), v) Peptides in *Bacillus* (Perego & Hoch 1996), vi) Peptidoglycan in *Myxococcus* (Kaplan & Plamam 1996), and vii) diketo piperazines (Holden et al. 1999).

In Gram-negative bacteria, the most widely studied QS signaling system is based on AHLs (Koutsoudis et al. 2006). The specificity of the AHL signals depends up on the length (typically 4–12 carbons) of the fatty acyl group, degree of saturation and substitution at carbon number 3 (carboxyl, hydroxyl, or fully reduced) of the acyl chain (Fuqua et al. 2001; Hoang et al. 2002; Watson et al. 2002; González & Marketon 2003; Wang et al. 2004). However, the variety of signals is limited (Ryan & Dow 2008; Schaefer et al. 2008; Decho et al. 2010). In contrast to the fatty AHL QS signals used by most Proteobacteria (Waters & Bassler 2005), *Rhodopseudomonas palustris* CGA009, *Bradyrhizobium* sp. BTAi1 and *Silicibacter pomeroyi* DSS-3 produce p-coumaroyl-HSL (aryl-HSL) QS signals (Larimer et al. 2004; Schaefer et al. 2008). The diversity QS systems are well illustrated by a single LuxI/R pair in *P. fischeri* (Schaefer et al. 1996), two AHL signal-receptor pairs in *P. aeruginosa* (Balaban et al. 2008), and three systems in *V. harveyi* (Henke & Bassler 2004). On the whole this system regulates more than 300 genes, primarily

implicated in virulence and biofilm formation (Soberón-Chávez et al. 2005; Schuster & Greenberg 2007).

Quorum-sensing system in Gram-positive bacteria—-*Bacillus subtilis, Enterococcus, S. aureus,* and *S. pneumoniae* (Firmicutes), and *Streptomyces* sp. (Actinobacillus) (Solomon et al. 1995; Park et al. 2005; Dunny 2007) operates through processed linear or cyclic oligopeptide signals (Solomon et al. 1995) and a two component regulatory system consisting of a membrane associated sensor histidine kinase and an intracellular response regulator (Hakenbeck & Stock 1996). In these bacteria, oligopeptides act as AIs, which contain side chain modifications such as isoprenyl groups in *B. subtilis* or thiolactone rings in *Staphylococcus* spp. (Otto et al. 1998; Ansaldi et al. 2002). QS in *Streptomyces* sp. is regulated by AIs such as γ-butyrolactones, which are structurally similar to AHLs of Gram-negative bacteria (Khmel & Metlitskaya 2006).

Another class of QS signaling system is a hybrid between the Gram-positive and Gram-negative systems. It was identified in the marine bacterium *V. harveyi* which has the ability to produce and detect two distinct AIs: AI-1 and AI-2 (Bassler et al. 1994) and a CAI-1 (Henke & Bassler 2004). Here, AI-1 is similar to AHL of Gram-negative QS (Cao & Meighen 1989), whereas AI-2 is a furanosyl borate diester, which does not show any resemblance to other AIs (Chen et al. 2002). In contrast to overlapping QS systems in *P. aeruginosa*, (Yarwood et al. 2005), QS signal mechanisms operate in parallel in *V. harveyi* and *B. subtilis* and act together to regulate target genes in a concerted manner (Miller et al. 2002; Mok et al. 2003).

Quorum Quenching: Mechanisms

A brief description of the QS process will enable us to appreciate the potential targets, which have been identified for inhibiting it. The most widely studied QS signaling system is based on AHLs (Figure 1) (Koutsoudis et al. 2006). The biosynthesis of AHL involves intermediates from fatty acid biosynthetic pathway: S-adenosyl methionine and an acylated acyl carrier protein (Schaefer et al. 1996). Gram-negative bacteria in general, employ two proteins, LuxI and LuxR during QS process. In the beginning of cell growth at low cell population densities, AHL synthase LuxI produces AHLs at low concentrations. These are diffused out of the cell. With increase in cell densities, AHLs above a threshold concentration in the environment are diffused back into the cell (Flagan et al. 2003). Here the QS signals bind to transcription regulator (LuxR) and activate the operon such as those responsible for virulence, and so on (Decho et al. 2010).

Several QQ strategies have recently been discovered in a few organisms primarily as a defense mechanism against competitors. The different QQ mechanisms operate by blocking different steps involved in QS. At low population densities, inhibition of signal generation and accumulation occurs by blocking fatty acid pathway. QQ mechanisms operating at high cell-population densities involve (i) R protein (Lux R type) inhibitor to prevent signal reception, (ii) AHL signal degradation enzymes, inhibitors for I and R proteins—autoinduction and activation and (iii) decay of the signal molecule (Dong et al. 2007).

Blocking signal generation and accumulation:

Two major potential targets identified in the synthesis of AHL-type signals are (i) enoyl-ACP reductase (ENR) and (ii) S-adenoysl methionine (SAM), substrate for the ENR enzyme (Zhang 2003; Dong et al. 2007). Triclosan, a widely used biocide, acts as an inhibitor of the enoyl-ACP reductase (Hoang and Schweizer, 1999), and Closantel inhibits histidine kinase sensor of 2 component system (Stephenson et al. 2000) to suppress AHL gene in vitro (Zhang 2003).

Preventing signal reception:

Inhibition of reception of signal molecule by antagonist molecule is another mechanism for controlling QS mediated infections (Antunes et al. 2009). These antagonist molecules compete or interfere with the binding of the signal molecule to the receptor. Inactivation of the receptor results in failure to express virulence factors. Diketopiperazines (DKP) are cyclic dipeptides which share structural similarity to signaling peptides in mammalian tissues (Draganov et al. 2005). They are produced by a range of bacteria (*P. aeruginosa, P. mirabilis, Citrobacter freundii* and *Enterobacter agglomerans*) (Holden et al. 1999) and yeast, fungi, and lichens (Draganov et al. 2000). DKP act as AHL antagonists in LuxR based QS and as agonists in others (Holden et al. 1999).

Inhibiting autoinduction and activation:

(i) Signal degradation

Three different mechanisms have been reported for degradation of QS signals: i) chemical, ii) metabolic, and iii) enzymatic. The chemical degradation has been reported primarily at alkaline pH, which leads to opening of the lactone ring (Yates et al. 2002) and results in loss of activity of the AHL signal in *Erwinia* (Byers et al. 2002). However, at acidic pH, the ring re-cyclizes and the activity gets restored. A few organisms such as *Variovorax paradoxus* and *P. aeruginosa* PAI-A have the ability to metabolize AHL to suppress QS bacteria and in the process they gain a competitive edge (Leadbetter & Greenberg 2000; Huang et al. 2003). Enzymatic degradation of QS signal molecules has been observed in a wide range of prokaryotes and a few eukaryotes (Figure 1, Table 1). Broadly, the QQ enzymes hydrolyze either the amide bond (Lin et al. 2003) or the lactone ring (Dong et al. 2000; Lee et al.

Table 1. Diversity of organisms targeting quorum sensing signals.

Organism	Enzyme and gene	Target[a]	Reference(s)
Bacillus sp.	AHL lactonase, *aiiA*	Short chain and long chain AHLs: C4HSL, C6HSL, C8HSL, C10HSL, 3OC4HSL, 3OC6HSL, 3OC8HSL, 3OC10HSL, 3OC12HSL, 3OHC4HSL	Dong et al. 2000; Dong et al. 2001; Fuqua et al. 2001
Bacillus thuringiensis	AHL lactonase, *aiiA*	AHL	Lee et al. 2002; Dong et al. 2004; Liu et al. 2005
Bacillus anthracis (expressed in *Burkholderia thailandensis*)	AHL lactonase, *aiiA*	C6HSL, C8HSL, C10HSL	Ulrich 2004
Bacillus cereus A24 (exprssed in *Pseudomonas aeruginosa* PAO1)	AHL lactonase, *aiiA*	AHL	Reimmann et al. 2002
Bacillus sp. (expression in plant pathogen *Erwinia carotovora*)	AHL lactonase, *aiiA*	AHL	Dong et al. 2000
Bacillus megaterium	Cytochrome P450 oxidation at ω-1, ω-2, and ω-3 of the acyl chain Lactonolysis, P450BM-3	AHLs and acyl homoserine	Chowdhary et al. 2007
Acidobacteria	AHL lactonase, *qlcA*	C6HSL, C7HSL, C8HSL	Riaz et al. 2008
Agrobacterium tumefaciens	AHL lactonase, *attM*	AHL	Zhang et al. 2002; 2004
Agrobacterium tumefaciens C58	AHL lactonase, *aiiB*	AHL	Zhang et al. 2002; Carlier et al. 2003; Zhang et al. 2004
Agrobacterium radiobacter K84	AHL lactonase, *aiiS*	AHL	Uroz et al. 2009
Arthrobacter sp. IBN110	AHL lactonase, *ahlD*	AHL	Reimmann et al. 2002; Park et al. 2003
Klebsiella pneumoniae KCTC2241	AHL lactonases, *ahlK*	AHLs: C6HSL, C7HSL, C8HSL	Park et al. 2003
Rhodococcus erythropolis W2	Lactonases (PTE family: Phosphotriesterase)[b], *qsdA*	AHLs: C6 to C14, with or without substitution at carbon 3	Uroz et al. 2008
	Oxidoreductase (converts to corresponding 3-hydroxy derivatives), *qsdA* (alleles)	C6HSL, 3OC6HSL, 3OC8HSL, C10HSL, 3OC10HSL, C12HSL, 3OC12HSL, 3OHC12HSL, 3OC14HSL AHL analogues: i) N-(3-oxo-6-phenylhexanoyl)HSL (aromatic acyl-chain substituent); ii) 3-oxo- dodecanomide (lacks HSL ring) [3OC12-NH_2]	Uroz et al. 2003; Uroz et al. 2005
	Amidolytic (cleaves the acyl chain) hydrolase	3OC10HSL	Uroz et al. 2005
Streptomyces sp. strain M664	AHL-acylase, *ahlM*	Effectively degrades AHLs (with chain length more than 8 carbon): C8HSL, C10HSL and 3OC12HSL Low activity on short-acyl-chain AHLs: C6HSL and 3OC6HSL	Park et al. 2005
Comomonas strain D1	AHL-acylase, Not known	N-AHSL with acyl-side chains |C4 to C16 with or without 3-oxo- or 3-hydroxy substitutions. C12HSL, 3OC12HSL, 3OHC12HSL, 3OC14HSL, 3OHC14:1-HSL, C16HSL	Uroz et al. 2007
Ralstonia eutropha XJ12A, XJ12B	AHL-acylase, *aiiD*	Long chain AHLs: 3OC8HSL, 3OC10HSL, 3OC12HSL Short chain AHLs with less efficiency	Lin et al. 2003
Ralstonia solanacearum GMI 1000	AHL-acylase, *aac*	Long chain AHL with acyl side chains >6C: C7HSL, C8HSL, 3OC8HSL, C10HSL	Chen et al. 2009
Shewanella sp. strain MIB015	AHL-acylase, *aac*	Long chain-AHLs:	Morohoshi et al. 2005

Table 1. continued on next page

Table 1. Continued.

Organism	Enzyme and gene	Target[a]	Reference(s)
Pseudomonas aeruginosa PAO1	AHL-acylase, *PA2385* (*qcs112/pvdQ*), *PA1032*	Long chain-AHLs: C7HSL, C8HSL, C10HSL, C12HSL	McClean et al. 1997; Huang et al. 2003; Uroz et al. 2003; Lamont & Martin 2003; Huang et al. 2006
Anabaena (Nostoc) sp. PCC 7120	AHL-acylase, *aiiC*	Long chain AHLs: OC12HSL,OC12HSL, OHC12-HSL, C14 HSL, OC14 HSL, OHC14HSLMedium chain AHLs: C10 HSL, OC10HSL, OHC10HSL	Romero et al. 2008
Laminaria digitata (Marine algae)	Haloperoxidases	3-oxo-AHLs	Borchardt et al. 2001
Delisea pulchra (Red algae)	Halogenated furanones	C6HSL and autoinducer (AI-2) [Furanosyl borate diester]	Givskov et al. 1996; 1997; Manefield et al. 1999; 2001; Ren et al. 2001; Hentzer & Givskov 2003; Delalande et al. 2005
Fungi: *Phialocephala fortinii, Ascomycetes, Meliniomyces variabilis*	Lactonase	C6HSL, 3OC6HSL	Uroz & Heinon 2008
Porcine kidney Acylase I.	AHL-acylase, *ACY1*	C4HSL, C8HSL	Xu et al. 2003
Eukaryotes: Human airway epithelial cells	Lactonase-like enzymes: Paraoxonases, PON1, PON2, PON3: *PON1*, *PON2*, *PON3*	Long chain AHLs: 3OC12-HSL of *P. aeruginosa*Less efficient with short chain AHLs: C6-HSL	Draganov et al. 2000; Chun et al. 2004; Hastings 2004
Recombinant PONs from human airway epithelial cells	Lactonase-like enzyme:PON2 Paraoxonases, *PON2: PON2*	DL-3OC6HSL, DL-C7HSL, DL-C12HSL, DL-C14HSL	Yang et al. 2005
Rabbit AiiA sp. antiserum	AHL lactonase, *aiiA*	3OC12HSL	Chun et al. 2004
Lotus corniculatus seedlings	Unknown	C6HSL, 3OC6HSL, 3OC8HSL, 3OC10HSL	Delalande et al. 2005

a: AHL: Acylhomoserine lactone, HSL: Homoserine lactone, C4HSL: N-butanoyl-L-HSL, C6HSL: N-hexanoyl HSL, C7HSL: N-heptanoyl-HL, C8HSL: N-octanoyl HSL, C10HSL: N-decanoyl HSL, C12HSL: N-dodecanoyl HSL, C14HSL: N-tetradecanoyl-HSL, C16HSL: N-hexadecanoyl-HSL, 3OC6HSL: 3-oxo-N-hexanoyl-HSL, 3OC8HSL: 3-oxo-N-octanoyl-HSL, 3OC10HSL: 3-oxo-N-decanoyl-HSL, 3OC12HSL: 3-oxo-N-dodecanoyl-HSL, 3OC14 HSL: 3-oxo-N-tetradecanoyl-HSL, OHC4HSL: 3-hydroxy-N-butanoyl-HSL, OHC10HSL: 3-hydroxy-N-decanoyl-HSL, OHC14HSL: 3-hydroxy-N-tetradecanoyl-HSL
b: QsdA belong to PTE of zinc dependent metallic proteins. It is unrelated either i) N-AHL lactones which belong to the Zinc-dependent glyoxylase family or N-AHSL amidohydrolases which belong to β-lactam acylases (Uroz et al. 2008).

2002) of AHL. The two reactions are largely mediated by the enzymes AHL-acylase, AHL-lactonase, lactonase like enzymes (paraoxonases), and oxidoreductases. A few cases of organisms possessing the enzymes acting as quenchers of QS signals have been presented below.

a) In prokaryotes

Bacteria belonging to the genus *Bacillus*–*B. anthracis, B. cereus*, *B. mycoides*, *B. subtilis*, *B. thuringiensis*, *Arthrobacter* spp., *Acidobacteria*, *Agrobacterium* spp., and *Klebsiella* spp. produce an enzyme—AHL-lactonase (AiiA) belonging to the superfamily—metallohydrolase. It hydrolyzes the lactone ring to form acyl-homoserine, which ceases to function as a QS signal (Dong et al. 2000, 2002, 2004; Lee et al. 2002; Park et al. 2003; Ulrich 2004; Liu et al. 2005; Thomas et al. 2005; Dong & Zhang 2005; Bai et al. 2008; Riaz et al. 2008; Uroz et al. 2009). In *Bacillus* AHL lactonases have a broad substrate specificity (Fuqua et al. 2001) but are quite selective for (s)-configuration (Thomas et al. 2005). *Bacillus* spp. could degrade *V. harveyi* AHL signal HAI-1 (Dong et al. 2002; Bai et al. 2008). Many homologues of this AHL-lactonase have been identified (Ulrich 2004) (Table 1) and expressed in different closely related species (Reimmann et al. 2002). Heterologous expression of the *B. cereus* strain A24 AiiA lactonase in *P. aeruginosa* PAO1 negatively affected quite a few QS controlled functions such as AHL accumulation, swarming motility and expression and secretion of virulence factors (Reimmann et al. 2002). The plant-colonizing bacterium *Pseudomonas fluorescens* carrying *aiiA* borne plasmid prevented soft rot disease in potatoes and egg plants (Dong et al. 2000) caused by *Pectobacterium carotovorum* (previously *Erwinia carotovora*) and crown gall disease caused by *A. tumefaciens* in tomatoes (Molina et al. 2003). Co-culturing *P. chlororaphis* with *Fusarium oxysporum* controls tomato vascular wilt caused by the latter. However, its co-culturing with AiiA-producing bacterium, *Bacillus* sp. A24 resulted in loss of its biocontrol activity (Molina et al. 2003). Similarly *aiiA* expression in transgenic tobacco plants made them less susceptible

to *P. carotovorum* (Dong et al. 2001). Phylogenetic studies have revealed that lactonase genes of *Bacillus* (*aiiA*) cluster together with *attM* (pAt plasmid borne) and *aiiB* (pTi plasmid borne) of *A. tumefaciens*, (Zhang et al. 2004) along with *aiiA* homologues from other α- and γ-Proteobacteria and an ORF from *Deinococcus radiodurans* (Carlier et al. 2003).

The enzyme AHL-acylase has also been reported from a wide range of prokaryotes belonging to Gram-positive and Gram-negative bacteria. The range of activities is relatively large in this case compared to that of AHL-lactonase, since AHLs have varying acyl-chain lengths, they provide variability of substrates to AHL-acylases (Table 1). AHL-acylase AiiD from *Ralstonia eutropha* strains are quite specific in their activity as they are more effective on long chain AHLs with chain length more than 8 carbons (Lin et al. 2003). In contrast, AHL-acylase of *Streptomyces* sp. strain M664 shows high efficiency with AHLs having chain length less than 8 carbons. The most interesting feature of this organism is the secretion of AHL-degrading enzyme into the culture medium, increasing the range of its action (Park et al. 2005). The diversity of organisms showing AHL-acylase has been widened by the work of Chen et al (Chen et al. 2009), who have recently shown that a putative aculeacin A acylase from *R. solnacearum* GMI1000 is an acylase with distinct QQ activity. *Comamonas* is yet another Gram-negative microbe which exhibited a wide range of AHL degradative patterns (Uroz et al. 2003), varying with acyl chain lengths between 4 and 16 carbon, with or without 3-oxo- or 3-hydroxy substitutions (Uroz et al. 2007). Quite a few alleles of AHL-acylase of *P. aeruginosa* PAO1 have preference for degrading long chain AHLs (Lamont & Martin 2003; Zhang & Dong 2004; Huang et al. 2006; Sio et al. 2006). The AHL-acylase type enzyme from filamentous nitrogen-fixing cyanobacterium *Anabaena* (*Nostoc*) sp. PCC7120 exhibits homology to the acylase QuiP of *P. aeruginosa* PAO1 (Romero et al. 2008). *Shewanella* sp. are known to possess acylase activities for AHL degradation (Morohoshi et al. 2005). Phylogentically, AHL-acylases share well conserved amino acid residues, which are important for autoproteolytic activities (Lin et al. 2003). The two residues important for their substrate specificity are Ile^{50} and Ser^{57} in *Ralstonia* sp. XJ12B (Lin et al. 2003), Leu^{50}- and Glu^{57} in *Actinoplanes utahensis* (Dong et al. 2007), Leu^{50} and Asp^{57} in *P. aeruginosa* PAO1 (Huang et al. 2003) and Leu^{50} and Ser^{57} in *Streptomyces* sp. (Park et al. 2005).

A series of studies have revealed that *Rhodococcus erythropolis* strains have a wide spectrum of QQ abilities (Table 1). *R. erythropolis* W2 has been reported to possess AHL-lactonase, oxidoreductase as well as AHL-acylase activities (Uroz et al. 2005, 2008; Park et al. 2006). *In vitro*, *R. erythropolis* W2 strongly interfered with AHL dependent violacein production by *C. violaceum* and transfer of pathogenicity in *A. tumefaciens*. In planta, *R. erythropolis* W2 markedly reduced pathogenicity of *P. carotovorum* sub sp. *carotovorum* in potato tubers (Uroz et al. 2003). AHLs were shown to be modified and degraded by amidolytic and novel oxidoreductase of *R. erythropolis* W2 (Uroz et al. 2005). *Acinetobacter* sp. has been shown to degrade C6HSL and C8 HSL, however much characterization is to be done (Kang et al. 2004).

Salmonella typhimurium, Escherichia coli, and *V. harveyi* produce AI-2 signals, which activate other genes leading to its metabolism and consequently inhibition of QSS (Taga & Bassler 2003; Xavier & Bassler 2005, Roy et al. 2009). LsrK (AI-2 kinase) phosphorylates AI-2 to phospho-AI-2, which confers a negative charge on AI-2. It restricts its reentry into the cell through Lsr transporter. Here quenching of the signal happens ex vivo and is advantageous since it is not limited by the need to overcome the barrier (the cellular membrane) (Roy et al. 2009).

b) In Eukaryotes

Human epithelial cells have enzymes paraoxonases PON1, PON2, and PON3 which exhibit important hydrolytic activity related to drug metabolism and detoxification of organophosphate (Ng et al. 2005; Dong et al. 2007). The capacity of human respiratory epithelia to inactivate *P. aeruginosa* QS signals was reported by Chun et al. (Chun et al. 2004). It was speculated that host defense mechanism targets 3OC12-HSL which is necessary for activation of *P. aeruginosa* QS C4-HSL system (Hastings 2004). Mammalian cells expressing three mouse paraoxonases (PONs) genes showed AHL degradation activities quite similar to that of lactonase enzymes (Yang et al. 2005). Human paraoxonases (PON1, PON2, and PON3) have lactonase activities with overlapping substrates but are quite specific as well. PON2 hydrolyzes and inactivates AHL, QS signals of pathogenic bacteria, whereas PON1 catalyzes the hydrolysis of aromatic and aliphatic lactones and lactonization of γ- and δ-hydroxy carboxylic acids. PON2 completely hydrolyzes 3OC6HSL (Draganov et al. 2005). Another interesting feature of the PON lactonases is their specificity to hydrolyze six-member ring lactones more efficiently than their 5-member ring analogs (Draganov et al. 2005). Expression of human paraoxonase showing lactonase activity in *Drosophila melanogaster* protected it from the lethality of *P. aeruginosa* (Stoltz et al. 2008). AHL inactivating activity was observed in the sera of mammalian animals including human and rabbit but not in chicken and fish (Draganov et al. 2000; Yang et al. 2005). These enzymes were less efficient on AHLs of short acyl chain lengths of 6 carbons (Chun et al. 2004; Yang et al. 2005).

Fungi such as *Phialocephala*, *Ascomycetes*, and *Melinimyces* have been shown to possess lactonase activity with ability to act upon the lactone ring of C6HSL and 3OC6HSL (Uroz & Heinon 2008). In addition to paraoxonases reported from animals, certain acylases from porcine kidney have also been recognized with ability to degrade AHLs (Reimmann et al. 2002; Xu et al. 2003). These findings although limited at present but are consistent with the idea that cells derived from human epithelia

tissue exposed to pathogens can inactivate the QS signal (Liu et al. 2005).

(ii) Antagonists

Antagonists molecules can compete or interfere with native AHL signal molecule for binding to Lux R-type receptor. This complex fails to activate QS signal transduction. Blocking the transduction through inhibitors of I and R proteins also helps in manipulating QSS (Antunes et al. 2009). AHLs with C10 and C12 acyl side chains can inhibit the C4HSL dependent expression of exproteases in *Aeromonas hydrophila* (Swift et al. 1999), violacein production in *C. violaceum* (McClean et al. 1997) and suppression of filament in pathogenic yeast *Candida albicans* (Hogan et al. 2004). 3OC12-HSL - AI produced by *P. aeruginosa* plays dual roles as QS signal and also as an effective bactericidal agent against Gram-positive bacteria (EC50 in the range of 22.1 to more than 100 μM) and not against Gram-negative (Kaufmann et al. 2005). 3OC12HSL from *P. aeruginosa* showed inhibitory effect on the production of exotoxins and cell wall fibronectin proteins and could also inhibit *agr* expression of *S. aureus*. 10 μM of 3OC12HSL completely inhibited growth dependent bioluminescence of *S. aureus* RN6390 (pSB2030) (Qazi et al. 2006). Human pathogen *S. aureus* is responsible for causing skin and lung infections. *S. aureus* group employ thiolactone-based auto-inducing peptide based QS to regulate *agr* virulence (Ji et al. 1997) and also to inhibit virulence in other *S. aureus* groups (categorized on the basis of their peptide sequences) (Ji et al. 1997; Schauder & Bassler 2001; Khmel & Metlitskaya 2006; Geisinger et al. 2008). In the human oral cavity, interaction between *S. gordonii* and *S. mutans* results in disruption of QS regulated bacteriocin production by the later, the organism causing dental caries (Fuqua et al. 2001). Fungi - *Penicillium radicicola* produce panicillic acid and *Penicillium coprobium* produce patulin to target LasR and RhlR QS regulators in *P. aeruginosa* (Koch et al. 2005; Rasmussen et al. 2005b). Plants such as tomato, pea, garlic are effective antagonists on LuxR based QS but not effective against *P. aeruginosa* (Teplitski et al. 2000; Rasmussen et al. 2005a). Bryozoan *Flustra foliacea* AHL act as antagonist to combat potential pathogenic bacteria (Peters et al. 2003).

Status of Quorum Sensing Inhibitors

(i) Natural

Natural compounds such as furanones and enones from the marine macro alga *Delisea pulchra* (Manefield et al. 2001; Ren et al. 2004) act by accelerating turnover of the LuxR protein there by lowering its availability to AHL. Furanones are structurally similar to HSLs and bind to LuxR-like proteins and thereby affecting the binding of the AI. This mechanism consequently results in reduced transcription (Manefield et al. 2002; Zhang 2003; Clatworthy et al. 2007). Furanone produced by marine alga *D. pulchra* consists of a fural ring structure with a substituted acyl chain at C-3 position and a bromine substitution at C-4 position. *D. pulchra* produces more than 30 different species of halogenated furanone compounds (de Nys et al. 1993), which quench the AHL molecules used by the pathogenic bacterium *Serratia liquefaciens* and *P. fischeri* (Givskov et al. 1996). The inactivation of AHL-mediated motility of *S. liquefaciens* MG1, results in preventing bacteria from colonizing within the algal cells (Eberl et al. 1996; Givskov et al. 1997; Manefield et al. 1999; Rasmussen et al. 2000). Oxidized halogens produced as a result of haloperoxidase activity in alga, *Laminaria digitata* react specifically with C3-oxo-AHLs and destroy their signaling ability by penetrating the biofilm (Borchardt et al. 2001). Similarly chloroperoxidases produced by marine algae also specifically inactivates C3-oxoAHLs. These enzymes thus prove microbicidal in nature (Taga & Bassler 2003). Natural furanones could enhance the survival rate of brine shrimps challenged with pathogenic *Vibrio* spp. at a concentration of 20 mg/l of cultured water (Defoirdt et al. 2006). It is however highly toxic to larvae at 50 mg/l and is too reactive to be used for treating bacterial infections (Hentzer & Givskov 2003; Defoirdt et al. 2006). *Chlamydomonas reinhardtii* can also interfere with QS by producing molecules which mimic bacterial QS signaling molecules (Teplitski et al. 2004).

Plants and animals which associate with microbes need to detect for their presence in a rapid and reliable manner (Mathesius et al. 2003). Among plant-microbial associations, *Medicago truncatula, Pisum sativum,* etc. develop a symbiotic relationship with AHL producing, nitrogen fixing bacterial symbiont—*Sinorhizobium meliloti* and *Rhizobium* sp. *P. sativum* and *M. truncatula* secrete substances, which mimic AHL signals to stimulate or inhibit AHL-regulated responses in bacteria (Cook 1999; Teplitski et al. 2000; Bauer & Robinson 2002; Gao et al. 2003; Mathesius et al. 2003) including *Pseudomonas* spp. (Marketon et al. 2002). Recombinant plants of potato and tobacco expressing lactonase (AiiA) could degrade AHLs and showed resistance to QS-dependent bacterial infection (Dong et al. 2000, 2001; Leadbetter & Greenberg 2000; Zhang et al. 2002; Lin et al. 2003). Recent studies have revealed the diversity of these systems and have shown that *Lotus corniculatus* seedlings exhibit some unique properties of stabilizing the AHL signal and may even inactivate them (Delalande et al. 2005).

Plants such as crown vetch, carrot, soybean, water lily, tomato, pea seedlings, habanero, and garlic produce compounds which can act as QSIs (Teplitski et al. 2000; Rasmussen et al. 2005a). Garlic extracts contain different QSIs (Rasmussen et al. 2005a), which show improved clearing and remarkable reduction in mortality of mouse lungs infected with *P. aeruginosa* (von Bodman et al. 2008). QSI compounds extracted from food sources especially garlic has been found to quite effective in inhibiting *in vitro* QS regulated biofilm during *P. aeruginosa* infections (Bjarnsholt et al. 2005). Bark of *Combretum albiflorum* contains flavan-3-ol catechin (a flavonoid) with abilities

to quench the production of QS-dependent factors such as pyocyanin and elastase and biofilm formation in *P. aeruginosa* (Vandeputte et al. 2010). Hamamelitannin, (2′,5-di-O-galloyl-D-hamamelose) a natural product present in the bark of *Hamamelis virginiana* was found to prevent device-associated Staphylococcal infections by acting as a QSI. It inhibits RNA III production, a component of agr QSS. The range of inhibition extended to infections caused by methicillin-resistant *Staphylococcus epidermidis* and *S. aureus* strains (Kiran et al. 2008).

Other natural QS inhibitors are fatty acids derived from ground beef and poultry meat (Roy et al. 2009), metabolites from plant extracts (Adonizio et al. 2008), and secondary fungal metabolite, Ambuic acid, which inhibits the biosynthesis of a cyclic peptide quormone in *S. aureus, Listeria innocua,* and *Enterococcus faecalis* (Nakayama et al. 2009).

(ii) Synthetic

The possible ways which can be envisaged for developing the chemical analogues of the AHL molecule to act as QS inhibitors (QSIs) are: a) substitution(s) in the acyl side chain; b) alteration(s) in the lactone ring; or c) changes in both the components. Acyclic or cyclic alkyl substituent especially those developed by replacing C3 with S in the acyl side chain resulted in analogues with ability to block the expression of LuxR- and LasR- controlled QS receptors (Olsen et al. 2002; Persson et al. 2005). Replacement of C-1 carbonyl group of the side chain with a sulphonyl group- Aryl substituent further enhanced the QSI activity (Castang et al. 2004). AHLs with C10 to C14 long acyl chains when substituted at C3, inhibited light output and growth in *S. aureus*. Incidentally, short chain AHLs did show any effect (Qazi et al. 2006). A significant reduction (from 50 to 90%) in the activity in *P. carotovorum* was recorded with AHL-analogs with extended acyl chain length (Chhabra et al. 1993). It was suggested that AHL analogs should be longer than the native AHL to act as efficient inhibitors (Hentzer & Givskov 2003). Specific N-acyl-cyclopentylamine (C_n-CPA) with an acyl chain length in the range of C_5–C_{10} showed strong inhibitory effects on Lux QSS. Its efficacy was higher than those recorded with halogenated furanones (Wang et al. 2008). C_{10}-CPA was most effective inhibitor on Las and Rhl based QS in *P. aeruginosa* (Ishida et al. 2007). C_9-CPA has been shown to be inhibitory to Spn QS of *Serratia marcescens* (Morohoshi et al. 2005) and *Aeromonas hydrophila* (Swift et al. 1999). Synthetic HSL derived sulfonyl ureas and N-phenylacytanoyl-L-HSL have been supported to inhibit Lux-QSS (Geske et al. 2007; Frezza et al. 2008). Another possibility is the introduction of unsaturated bond near the amide bond, which was shown to completely abolish bonding of the QS signals to the receptor (Chhabra et al. 1993). Analogues with variation in the length of acyl side chain of 3OC12HSL as in the 3OC12-(aminocyclohexanone) could strongly influence the two QS systems of *P. aeruginosa* (Smith et al. 2003a; Rasmussen & Givskov 2006b) by inhibiting the QS regulated expression of *plasI-gfp* fusion and virulence factors (Smith et al. 2003a). Replacing phenol ring with a hexanone ring 3OC12-(2-aminophenol) led to a further improvement in the efficacy of this compound, which act as a potent inhibitor of QS controlled LasR in *P. aeruginosa* (Smith et al. 2003b). Synthetic signal analogues containing lactones or lactam rings alone were found to be effective as inhibitors of Staphylococcal infections (Winans & Bassler 2002; Lyon & Novick 2004). Softening of bacterial biofilms by the action of these compounds made them more susceptible to conventional antibiotics and the action of host immune system (Rasmussen & Givskov 2006b).

Screening of a library of compounds such as 4-nitropyridine-N-oxide (4-NPO), indole, p-benzoquinone, 2,4,5-tribromoimidazole, indole and 3-nitrobenzene sulphone amide proved quite effective in reducing the expression of the QS regulated genes in *P. aeruginosa* (Rasmussen et al. 2005a). Prof. Greenberg's group identified small molecules inhibitors of LasR (Mattmann et al. 2008), which function as agonists for QscR, which is critical for pathogenic abilities of *P. aeruginosa* (Fuqua 2006) and can be exploited to reduce the virulence caused due to the expression of LasR and QscR (von Bodman et al. 2008). Synthetic analog, N-phenyl-4-{[(phenylamino) thioxomethyl]amino}-benzenesulfonamide was identified from a library of small organic molecules for its ability to inhibit the binding of the QS signal (norepinephrine) to its adrenergic receptor QseC. This resulted in inhibition of the expression of virulence genes and reduced morbidity and mortality in a wide range infection models (Rasko et al. 2008). Similarly, antibody RS2-1G9 protects macrophages from cytotoxic effects of the *P. aeruginosa* QS signal (3OC12HSL) (Kaufmann et al. 2008). Efforts to inhibit the synthesis of QS signal molecule (AI-2) by employing synthetic analogues at submicromolar range have helped to increase the chances of successful application of this strategy (Alfaro et al. 2004; Shen et al. 2006). Anthranilate analog represses PQS production but does not affect bacterial growth. Methyl-anthranilate caused dose dependant reduction in elastase activity of *P. aeruginosa* PAO1 (Calfee et al. 2001). It has raised the possibilities for novel anti-infective therapies (Williams 2002; Sio et al. 2006).

Quite a few efforts have gone in to modulate QS to reduce the production of toxins or to activate the QS at low cell density. It will provide an opportunity to the immune system to attract them (Martin et al. 2008). These have resulted in potential QS-modulating therapies such as macrolide antibiotics, QS vaccines and competitive QS inhibitors (Martin et al. 2008).

Microlides such as azithromyzin inhibit QS (Tateda et al. 2001) by reducing the production of several virulence factors of *P. aeruginosa*, such as elastase, rhampolipids and alginate synthesis (Ichimiya et al. 1996; Imamura et al. 2004; Nalca et al. 2006). Azithromycin acts by reducing LasI and RhlI, leading to reduction in HSL by 94% and 72%, respectively and consequently virulence in

P. aeruginosa (Imamura et al. 2004; (Tateda et al. 2001) especially in cystic fibrosis cases (Saiman et al. 2003). It inhibits QS at sub-inhibitory concentrations (Nalca et al. 2006). Its chemically related antibiotics, erythromycin and Clariothromycin affect HSL production and reduce production of virulence factors such as protease and elastase (Molinari et al. 1993; Mizukane et al. 1994; Sofer et al. 1999). Virstatin inhibits the *V. cholerae* Tox T, transcriptional regulator involved in the expression of virulence factors (i) the toxin—coregulated pilus and (ii) cholera toxin. Administration of virstatin during *in vivo* experiments on infant mice, protected its intestine from *Vibrio cholerae* (Hung et al. 2005).

Furanones with varied side chain lengths and substitution in the ring structure particularly those compounds which lacked a side chain but had a electronegative substituent on the furanone ring effectively inhibited the QSS of *P. aeruginosa* (Hentzer et al. 2002; Manefield et al. 2002). Halogenated furanones were found to inhibit the production of carbapenem (in *E. carotovora*) by regulating Lux R homolog CarR (Manefield et al. 2001). A halogenated furanone derivative, (5Z)-4-bromo-5-(bromomethylene)-3-butyl-2(5H-furanone) was found to inhibit biofilm formation and swarming motility in *E. coli* and *B. subtilis* (Ren et al. 2001; 2002). Four synthetic furanones were found to significantly affect biofilm formation by *S. epidermidis* (Lonn-Stenrud et al. 2009). Since two of the furanones: (Z)-5-(bromomethylene) furan-2(5H)-one and (Z)-3-bromo-5-(bromomethylene) furan-2(5H)-one were found to be non-irritative and non-genotoxic, they represented promising therapeutic agents for protecting surface colonization by *S. epidermidis* (Lonn-Stensrud et al. 2009). Of the two synthetic furanones, the former appeared to inhibit AI-mediated QS and decrease the severity of mice lung infections caused by *P. aeruginosa* (Wu et al. 2004). Compared to natural furanones, the efficiency of synthetic analogues such as C30 and C56 with varying side chain length and substitutions were found to be effective in inhibiting QSS of *P. aeruginosa* (Hentzer et al. 2002; 2003). The effectiveness of furanone (compound C-30) treated biofilms of *P. aeruginosa* was evident by higher susceptibility of biofilms to tobramycin in comparison to untreated ones (Hentzer et al. 2002; 2003). *Vibrio anguillarum* treatment with furanone C-30 significantly reduced the mortality of rainbow trout (Rasch et al. 2004). Halogenated furanones specifically inhibits bacterial QS, such as surface colonization by *Serratia liquefaciens* (Givskov et al. 1996).

Analog of SAM such as S-adenosylhomocysteine, 8-adenosyl cysteine and sinefungin act as inhibitors of AHL synthesis (catalyzed by *P. aeruginosa* RhlI protein) (Parsek et al. 1999). Imine adduct resulting from the condensation of a halogenated salicylaldehyde and 3-aminoacetophenone affected the transcription of T3SS without affecting other important properties like growth or motility in *E. coli* EPEC (Gauthier et al. 2005). QSI, RNAIII-inhibiting peptide has been found to effectively inhibit phosphorylation of TRAP (Target of RAP), in animal model infected with *S. aureus* (Gov et al. 2001; Balaban et al. 2007). This antagonism of RAP has the potential to act as therapeutic is exciting but its future is still unclear (Martin et al. 2008). Its potential appears to lie in preventing biofilms formed by *S. epidermidis* (Joelsson et al. 2006). The promise of RIP was evident from the augmentation in the antibacterial action of ciprofloxin, imipenem, and vancomycin (Cirioni et al. 2006).

Structural mimics of signal molecules such as synthetic AI peptides interfere with signal binding to the receptor (Lyon et al. 2000]. Analog of QS signal—HSL, [N-(2-oxocyclohexyl)-3-oxododecanamide)] were found to antagonize HSL activity which consequently lead to reduction in *P. aeruginosa* induced pyocyanin, elastase and biofilm formation (Smith et al. 2003a). A high throughput screening of 150,000 small organic compounds lead to the identification of LED 209 (N-phenyl-4-[(phenylamino)thioxomethyl]amino]-benzene sulfonamide) (Rasko et al. 2008). It blocks the binding of signals - (i) AI-3 (a bacterial autoinducer produced by normal gut intestinal flora) and (ii) epinephrine/norepinephrine (hormones produced by the host) (Sperandio et al. 2003)—to QseC (membrane bound sensor kinase) mediated activation of virulence gene expression in entero hemorrhagic *E. coli* (EHEC) (Walters & Sperandio 2006). The scope of such small molecules could be highly valuable as pathogenic blockers (Njoroge & Sperandio 2009) in the treatment of EHEC infections since QseC homologues have been found to be present in more than 25 microbial pathogens of significance to humans and plants (Rasko et al. 2008).

More recent approach to target oral microbial pathogens such as *Streptococcus mutans* and related species has been through a novel class of antimicrobials, called specifically-targeted antimicrobials peptides (STAMPs) (Eckert et al. 2006). STAMPSs are made up of two functionally independent linearly arranged peptide moities. These have a very strong potential to develop into novel therapeutics (Li et al. 2010).

AHL sequestration by antibodies

Biochemical studies have revealed the effect of AHL such as 3-oxo-C12-HSL on mammalian cells. It promotes induction of apoptosis in macrophages and neutrophils (Tateda et al. 2003). Kaufmann et al. pioneered an immuno-pharmacotherapeutic approach to QS mediated microbial infections by developing anti-AHL monoclonal antibodies (mAbs). They demonstrated the inhibitory effect of mAb RS2-1G9 on AHL based QS in *P. aeruginosa* (Kaufmann et al. 2006). Further efforts have been made on the synthesis of QQ catalytic antibodies (sulfones) which resemble the transition-state structure of AHL-ring hydrolysis leading to attenuation of bacterial virulence (Kapadnis et al. 2009). 3-oxo-C_{12}-HSL–protein conjugate based immunization in mice proved effective in preventing motility caused by *P. aeruginosa* infections (Miyairi et al. 2006).

Metals targeting QS

Metals have been found to affect biofilm related activities. Ionic silver has antibacterial properties which affect *P. aeruginosa* caused infections (Melaiye et al. 2005), where as Gallium acts by interfering with iron metabolism (Banin et al. 2008; Patriquin et al. 2008) to prevent biofilm formation (Yamamoto et al. 1994; Banin et al. 2005, 2006). Nitric oxide is a reactive free radical which kills cells within established biofilms (Barraud et al. 2006; Ghaffari et al. 2006; Hetrick et al. 2008; Hetrick et al. 2009).

Potential anti-bacterial opportunities

Bacteria are highly adaptive to fluctuations in environmental conditions (Zhang & Dong 2004), which enable them to coexist and co-evolve in natural environments, symbiotically or even as pathogen with their host. The worry which looms large on our minds is the ever increasing resistance of pathogens to antibiotics (Marris 2006; Cars et al. 2008; Courvalin 2008; Defoirdt et al. 2008). The focus is largely on *P. aeruginosa*, which causes life-threatening infections such as cystic fibrosis, leading to high rates of morbidity and mortality among human beings (Lyczak et al. 2002). The solution to this problem can be found out by understanding bacterial behaviour particularly in the case of chronic infection diseases. Here, bacteria prefer to remain silent and evade human immune responses (Otto 2004) until they have reached a cell density sufficient enough to produce enzymes which can destroy the host cell (Schauder & Bassler 2001; Winans & Bassler 2002; Waters & Bassler 2005). Quite a few examples of organisms with an ability to counter this phenomenon and retarding the expression of virulent behaviour of these pathogens have given some hope of finding a solution to this problem. The possibilities of succeeding lies either with a microbe (natural isolates or genetically engineered) or genetically engineer plants (Ferrer-Miralles et al. 2009), for producing QQ molecules. These molecules should be highly specific to QS regulator, stable, resistant to degradation by the host (Rasmussen & Givskov 2006b), versatile in production and non-toxic (Rasmussen & Givskov 2006a). Alternatively, a combination of QS signal degrading molecules may be exploited (Dong et al. 2000; 2001; Reimmann et al. 2002; Uroz et al. 2003). This method can be complemented by saturating a given environment with AHL molecules (Fray et al. 1999; Mae et al. 2001; Fray 2002) to initiate QS at a suboptimal cell density, which will be detrimental for the survival of pathogenic bacteria. Engineering plants with ability to induce QS at sub-optimal bacterial population has shown mixed behaviour among the non-target microbial community in the rhizosphere: i) *yenI* (from *Yersinia enterocolitica*) encoding for AHL synthase in the chloroplast of transgenic plants resulted activation of QS of *Erwinia* and *Pseudomonas* with the release of QS signaling molecules (Fray et al. 1999; Dong et al. 2001; Mae et al. 2001; Fray 2002), ii) a negative impact of AHL produced by plants and bacteria was the reduction in biocontrol ability of *Pseuodmonas aureofaciens* (Fray et al. 1999), and iii) a no evident impact of rhizospheric microbial populations was recorded by C6HSL and 3OC6HSL signals produced by transgenic tobacco plants (D'Angelo-Picard et al. 2004).

C. albicans, a fungal pathogen is normally a component of human microflora. However, in immunocompromised individuals, they can cause systemic candidiasis. In mixed infections, it is often associated with *P. aeruginosa*. Within the conducive host physiological conditions, *C. albicans* turns virulent and invasive upon transformation from a budding to a hyphal morphology (Dhillon et al. 2003). At this stage, the farnesol produced by *C. albicans* interferes with the quinolone signal specific QS system in *P. aeruginosa*. In the presence of farnesol, the *Pseudomonas* quinolone signal binding with pqsA promoter (which regulates expression of virulence factors) (Déziel et al. 2005) is non-productive (Calfee et al. 2001). Farnesol at a concentration level of 25 μM lead to 39% reduction in PQS and at a concentration of 250 μM resulted in 85% decrease in extracellular PQS levels. Consequently, 250 μM farnesol to the medium of *P. aeruginosa* strain PA14 cultures resulted in 72% reduction in pyocyanin (a redox-active phenazine) production and 95% in the case of *P. aeruginosa* PAO1 in comparison to the control cultures. It thus has the potential to control *Pseudomonas* infection by blocking the production of virulence factor without inhibiting its growth. This places farnesol in the class of QS inhibitory molecules (Cugini et al. 2007). These studies demonstrate that strategies which affect the virulence process or the ability of bacteria to modulate the host immune system (Dunn et al. 2009) hold promise for effective management of chronic bacterial infections.

Limitations of QSI

Most of the QQ effects have been recorded on non-mucoid *P. aeruginosa*, which is observed in early stages of pulmonary infection in CF patients. Chronic patients have mucoid *P. aeruginosa*, which may not be cured through QSI treatments (Bjarnsholt & Givskov 2007). Halogenated furanones exhibit toxic side effects with potential to cause cancer and is likely to be unsuitable for human beings (Bjarnsholt & Givskov 2007), due to their base labile nature and are substrates for mammalian paraoxonases (Yates et al. 2002; Dragnov et al. 2005; Yang et al. 2005). In certain situations such as blocking the agr system leads to increased biofilm formation along with enhanced antibiotic resistance (Vuong et al. 2000, 2004). Thus targeting agr system to control staphylococcal infections may be counterproductive (Harraghy et al. 2007).

Selective pressure and QSI resistance

The basic science is being revealed for most QSIs and incidentally the efforts during the past two decades have not led them to be in the clinical stage. Since G+ve and G-ve bacteria do not show similarity in their QSS and does not communicate at high frequency, the chances of a broad spectrum QSI are bleak Bjarnsholt & Givskov 2008).The basic assumption and emphasis has been that disruption of QS is unlikely to put harsh selective pressures on pathogenic microbes, which are thus "unlikely" to develop resistance to QSIs (Hentzer & Givskov 2003; Defoirdt et al. 2010). However, it will be premature to assume that bacteria will not develop resistance against QSIs, such that we may not see an end to this battle against infections (Bjarnsholt & Givskov 2008). Quite a few cases provide evidences to support the likelihood of development of QSI resistance among pathogenic microbes: (i) variation in the specificity of AHL synthases in *E. carotovora* strains SCC3193 and SSC1 (Brader et al. 2005), (ii) variability in the presence of signal receptors in *Burkholderia mallei*—2-5 LuxR homologs (Case et al. 2008). Point mutations in the receptor of LuxR signal make them insensitive to N-(propylsulfanylacetyl)-L-HSL. This synthetic antagonist acts as an agonist for the mutant form (Koch et al. 2005). Further support follows from high mutation rate in the QS of different *V. cholerae* strains, which lead to constitutive or even non-functional QS regulation (Joelsson et al. 2006). The occurrence of QSS on a transposon in *S. marcescens* provide it with an opportunity to overcome any disruption in their QSS (Wei et al. 2006). Finally, Diggle et al. have shown the influence of nutrient medium on the growth of wild type and *lasI* and *lasR* mutants of *P. aeruginosa* (Diggle et al. 2007). These evidences have led to the apprehension that pathogenic microbes may exploit their genetic reservoir to develop resistance to QSI treatment. In view of the limited discoveries leading to novel modes of action against hospital pathogens, it has been estimated that it may take 10–15 years before novel antimicrobials are made available (Clatworthy et al. 2007; Payne et al. 2007). Prof. Givskov feels that it will take 5–10 years before QSI drugs can be seen in the market (Bjarnsholt & Givskov 2008). Although many of these compounds are quite promising, their clinical utility is yet to be proven. They however, expand the range of well and urgently needed armamentarium against highly resistant microbes (Martin et al. 2008). The need is to expand our strategies to find novel anti-microbials and anti-virulence targets (Njoroge & Sperandio 2009).

Opinion

QQ may be effective in disturbing the biofilm structure and increasing its susceptibility to the action of antibiotics (de Kievit & Iglewski 2000; Dong et al. 2000; Parsek & Greenberg 2000; Ren et al. 2001; Lin et al. 2003; Ueda & Wood 2009). However, caution need to be exercised on the practical application of this strategy (Hibbing et al. 2009) as non-biofilm cells (of *P. aeruginosa*) are much more likely to express their virulence factors, toxins and proteases than non-planktonic cells in the biofilm (Resch et al. 2005). It may also be realized that a conclusive relation between QQ and its exploitation for gaining competitive advantage has not been established (Hibbing et al. 2009). So far, the approach of QS inhibition has met with limited success (Otto 2004; Wu et al. 2004; Persson et al. 2005; Rasmussen et al. 2005a), however, it has the potential to allow us to overcome the problem of rapidly evolving multi-drug resistant bacteria (Alksne & Projan 2000). It has been proposed that in natural environments, such altered signal molecules may provide cells with important sensory information about their physiochemical conditions (Decho et al. 2010). Such studies suggest that the most effective treatment regimen may be a combination of antibiotics and QSIs (Rasmussen et al. 2005a). The long-term goal of such studies is to develop novel biocontrol agents (Fray 2002; Hentzer et al. 2003; Bjarnsholt & Givskov 2008; Uroz et al. 2009), therapeutic strategies (Cámara et al. 2002), directed at infection control in both plants and animals (Uroz et al. 2005), and to effectively prevent widespread epidemic outbreaks.

Rhodococcus, *Comomononas, Pseudomonas,* and *Ralstonia* spp. are among the top contenders as organisms which may be exploited in the future as a source of QQ enzymes. It is primarily because of their abilities to quench a wide range of QS signals with varying acyl side chain lengths. However, the dependence of their QQ activity upon the chain length of the AHL molecules can be regarded as a major limiting factor in using them as "universal" antipathogenic drug producers. The best target may be to disrupt the QS signals outside the cell and here AHL lactonase may be the best approach since it is active against a wide range of AHLs with little influence of the length of the acyl chain on its efficiency (Dong et al. 2008). Here, *Bacillus* is more likely to succeed as an organism of choice because they produce AHL-lactonases, whose QQ activity is not limited by acyl chain length or substitutions at C3 position (Uroz et al. 2009). Another very interesting feature reported recently has been the high frequency of AHL based QS systems among Proteobacteria (Case et al. 2008). It has also revealed that quite a few organisms have the potential to detect and respond to exogenous signals, though they themselves are not able to produce QS signals as they lack genes for AHL synthase (Case et al. 2008). *Bacillus* being independent of AHL type QS (the only reported exception is that of Ren et al. 2002), AHL-lactonase will not prove inhibitory to itself. On the other hand, it can affect not only the QS of the AHL producers but also those which are non-AHL producers including the orphan QS systems (Fuqua 2006; Case et al. 2008; Decho et al. 2010). In addition, *Bacillus* can be used in a wide range of environments including treatment of human beings, as it is a known probiotic organism, which has been accorded the status of GRAS:

generally regarded as safe by FDA (Porwal et al. 2009). Furthermore, because of its ability to sporulate and a capacity to produce a range of antibiotics, it is less susceptible to attack by antibacterial agents and other antibiotic producing organisms (Arguelles-Arias et al. 2009). It is further recommended that plant or algal extracts might pose relatively less risk of QSI resistance development (Defoirdt et al. 2010) and it may be better to target major virulence factors instead of blocking their expression (Clatworthy et al. 2007; Charkowski 2009). Quorumex's first product (Topic-Qx), from plant materials claims to have anti-QS properties. Incidentally, it has met with a very aggressive response from public, who have shown apprehensions about its utility and authenticity (http://www.boingboing.net/2010/06/22/do-quorum-sensing-me.html).

Declaration of interests

We are thankful to Directors of Institute of Genomics and Integrative Biology, CSIR; National Environmental Engineering Research Institute, CSIR grant SIP 16 for providing necessary funds, facilities and moral support.

References

Adonizio, A, Kong, KF, Mathee, K. (2008). Inhibition of quorum sensing-controlled virulence factor production in *Pseudomonas aeruginosa* by south Florida plant extracts. Antimicrob Agents Chemother, 52, 198–203.

Alfaro, JF, Zhang, T, Wynn, DP, Karschner, EL, Zhou, ZS. (2004). Synthesis of LuxS inhibitors targeting bacterial cell–cell communication. Org Lett, 6, 3043–3046.

Alksne, LE, Projan, SJ. (2000). Bacterial virulence as a target for antimicrobial chemotherapy. Curr Opin Biotechnol, 11, 625–636.

Ansaldi, M, Marolt, D, Stebe, T, Mandic-Mulec, I, Dubnau, D. (2002). Specific activation of the *Bacillus* quorum-sensing systems by isoprenylated pheromone variants. Mol Microbiol, 44, 1561–1573.

Antunes, LCM, Ferreira, RBR. (2009). Intercellular communication in bacteria. Critical Rev Microbiol, 35, 69–80.

Arguelles-Arias, A, Ongena, M, Halimi, B, Lara, Y, Brans, A, Joris, B, Fickers, P. (2009). *Bacillus amyloliquefaciens* GA1 as a source of potent antibiotics and other secondary metabolites for biocontrol of plant pathogens. Microbial Cell Fact, 8, 63.

Baca-DeLancey, RR, South Mary, MT, Ding, X, Rether, PN. (1999). *Escherichia coli* genes regulated by cell-to-cell signaling. Proc Natl Acad Sci USA, 96, 4610–4614.

Bai, F, Han, Y, Chen, J, Zhang, X-H. (2008). Disruption of quorum sensing in *Vibrio harveyi* by the AiiA protein of *Bacillus thuringiensis*. Aquaculture, 274, 36–40.

Balaban, N, Cirioni, O, Giacometti, A, Ghiselli, R, Braunstein, JB, Silvestri, C, Mocchegiani, F, Saba, V, Scalise, G. (2007). Treatment of *Staphylococcus aureus* biofilm infection by the quorum sensing inhibitor RIP. Antimicrob Agents Chemother, 51, 2226–2229.

Balaban, N, Givskov M, Rasmussen, TB. (2008). *In vivo* studies: Inhibiting biofilm-associated bacterial infections using QSIs. Ed. N. Balaban In: Control of biofilm infections by signal manipulation, vol. 2, Berlin, Heidelberg: Springer, 119–129.

Banin, E, Brady, KM, Greenberg, EP. (2006). Chelator-induced dispersal and killing of *Pseudomonas aeruginosa* cells in a biofilm. Appl Environ Microbiol, 72, 2064–2069.

Banin, E, Lozinski, A, Brady, KM, Berenshtein, E, Butterfield, PW, Moshe, M, Chevion, M, Greenberg, EP, Banin, E. (2008). The potential of desferrioxamine-gallium as an anti-*Pseudomonas* therapeutic agent. Proc Natl Acad Sci USA, 105, 16761–16766.

Banin, E, Vasil, ML, Greenberg, EP. (2005). Iron and *Pseudomonas aeruginosa* biofilm formation. Proc Natl Acad Sci USA, 102, 11076–11081.

Barraud, N, Hassett, DJ, Hwang, SH, Rice, SA, Kjelleberg, S, Webb, JS. (2006). Involvement of nitric oxide in biofilm dispersal of *Pseudomonas aeruginosa*. J Bacteriol, 188, 7344–7353.

Bassler, BL, Wright, M, Silverman, MR 1994. Multiple signalling systems controlling expression of luminescence in *Vibrio harveyi*: sequence and function of genes encoding a second sensory pathway. Mol Microbiol, 13, 273–286.

Bauer, WD, Robinson, JB. (2002). Disruption of bacterial quorum sensing by other organisms. Curr Opin Biotechnol, 13, 234–237.

Bjarnsholt, T, Givskov, M. (2007). Quorum-sensing blockade as a strategy for enhancing host defences against bacterial pathogens. Phil Trans R Soc Lond B Biol Sci 362, 1213–1222.

Bjarnsholt, T, Givskov, M. (2008). Quorum sensing inhibitory drugs as next generation antimicrobials: worth the effort?'. Curr Infect Disease Reports, 10, 22–28.

Bjarnsholt, T, Jensen, PO, Rasmussen, TB, Christophersen, L, Calum, H, Hentzer, M, Hougen, HP, Rygaard, J, Moser, C, Eberl, L, Høiby, N, Givskov, M. (2005). Garlic blocks quorum sensing and promotes rapid clearing of pulmonary *Pseudomonas aeruginosa* infections. Microbiol, 151, 3873–3880.

Borchardt, SA, Allain, EJ, Michels, JJ, Stearns, GW, Kelly, RF, McCoy, WF. (2001). Reaction of acylated homoserine lactone bacterial signaling molecules with oxidized halogen antimicrobials. Appl Environ Microbiol, 67, 3174–3179.

Brader, G, Sjöblom, S, Hyytiöinen, H, Sims-Huopaniemi, K, Palva, ET. (2005). Altering substrate chain length specificity of an acylhomoserine lactone synthase in bacterial communication. J Biol Chem, 280, 10403–10409.

Byers, JT, Lucas, C, Salmond, GP and Welch, M. (2002). Nonenzymatic turnover of an *Erwinia carotovora* quorum–sensing signaling molecule. J Bacteriol 184, 1163–1171.

Calfee, MW, Coleman, JP, Pesci, EC. (2001). Interference with *Pseudomonas* quinolone signal synthesis inhibits virulence factor expression by *Pseudomonas aeruginosa*. Proc Natl Acad Sci USA, 98, 11633–11637.

Cámara, M, Williams, P, Hardman, A. (2002). Controlling infection by tuning in and turning down the volume of bacteria small-talk. Lancet Infect Dis 2, 667–676.

Cao, JG, Meighen, EA 1989. Purification and structural identification of an autoinducer for the luminescence system of *Vibrio harveyi*. J Biol Chem 264, 21670–21676.

Carlier, A, Uroz, S, Smadja, B, Fray, R, Latour, X, Dessaux, Y, Faure, D. (2003). The Ti plasmid of *Agrobacterium tumefaciens* harbors an attM-paralogous gene, *aiiB*, also encoding N-acyl homoserine lactonase activity. Appl Environ Microbiol, 69, 4989–4993.

Cars, O, Högberg, LD, Murray, M, Nordberg, O, Sivaraman, S, Lundborg, CS, So, AD, Tomson, G. (2008). Meeting the challenge of antibiotic resistance. Br Med J, 337, 726–728.

Case, RJ, Labbate, M, Kjelleberg, S. (2008). AHL-driven quorum-sensing circuits: their frequency and function among the Proteobacteria. ISME J, 2, 345–349.

Castang, S, Chantegrel, B, Deshayes, C, Dolmazon, R, Gouet, P, Haser, R, Reverchon, S, Nasser, W, Hugouvieux-Cotte-Pattat, N, Doutheau, A. (2004). N–Sulfonyl homoserine lactones as antagonists of bacterial quorum sensing. Bioorg Med Chem Lett, 14, 5145–5149.

Charkowski, AO. (2009). Decaying signals: will understanding bacterial-plant communications lead to control of soft rot? Curr Opin Biotechnol, 20, 178–184.

Chen, C-N, Chen, C-J, Liao, C-T, Lee, C-Y. (2009). A probable aculeacin A acylase from the *Ralstonia solanacearum* GMI1000 is N-acyl-homoserine lactone acylase with quorum–quenching activity. BMC Microbiol, 9, 89.

Chen, L, Wang, R, Zhou, T, Kazuyuki, A. (2005). Noise-induced cooperative behavior in a multicell system. Bioinformatics 21, 2722–2729.

Chen, X, Schauder, S, Potier, N, Van Dorsselaer, A, Pelczer, I, Bassler, BL, Hughson, FM. (2002). Structural identification of a bacterial quorum-sensing signal containing boron. Nature 415, 545–549.

Chevrot, R, Rosen, R, Haudecoeur, E, Cirou, A, Shelp, BJ, Ron, E, Faure, D. (2006). GABA controls the level of quorum-sensing signal in *Agrobacterium tumefaciens.* Proc Natl Acad Sci USA, 103, 7460–7464.

Chhabra, SR, Stead, P, Bainton, NJ, Salmond, GP, Stewart, GS, Williams, P, Bycroft, BW 1993. Autoregulation of carbapenem biosynthesis in *Erwinia carotovora* by analogues of *N*-(3-oxohexanoyl)-L-homoserine lactone. J Antibiot (Tokyo), 46, 441–454.

Chowdhary, PK, Keshvan, N, Nguyen, HQ, Peterson, JA, González, JE, Haines, DC. (2007). *Bacillus megaterium* CYP102A1 oxidation of acyl homoserine lactones and acyl homoserines. Biochem, 46, 14429–14437.

Chun, CK, Ozer, EA, Welsh, MJ, Zabner, J, Greenberg, EP. (2004). Inactivation of a *Pseudomonas aeruginosa* quorum-sensing signal by human airway epithelia. Proc Natl Acad Sci USA, 101, 3587–3590.

Cirioni, O, Giacometti, A, Ghiselli, R, Dell'Acqua, G, Orlando, F, Mocchegiani, F, Silvestri, C, Licci, A, Saba, V, Scalise, G, Balaban, N. (2006). RNAIII-inhibiting peptide significantly reduces bacterial load and enhances the effect of antibiotics in the treatment of central venous catheter–associated *Staphylococcus aureus* infections. J Infect Dis, 193, 180–186.

Clatworthy, AE, Pierson, E, Hung, DT. (2007). Targeting virulence: a new paradigm for antimicrobial therapy. Nat Chem Biol, 3, 541–548.

Cook, DR. (1999). *Medicago truncatula* – a model in the making! Curr Opin Plant Biol, 2, 301–304.

Courvalin, P. (2008). Predictable and unpredictable evolution of antibiotic resistance. J Internal Med, 264, 4–16.

Cugini, C, Calfee, M, Farrow III, JM, Morales, DK, Pesci, EC, Hogan, DA. (2007). Farnesol, a common sesquiterpene, inhibits PQS production in *Pseudomonas aeruginosa*. Mol Microbiol, 65, 896–906.

Czajkowski, R, Jafra, S. (2009). Quenching of acyl–homoserine lactone–dependent quorum sensing by enzymatic disruption of signal molecules', Acta Biochimica Polonica, 56, 1–16.

D'Angelo–Picard, C, Faure, D, Carlier, A, Uroz, S, Raffoux, A, Fray, R, Dessaux, Y. (2004). Bacterial populations in the rhizosphere of tobacco plants producing the quorum–sensing signals hexanoyl–homoserine lactone and 3-oxo-hexanoyl-homoserine lactone. FEMS Microbiol Ecol, 51, 19–29.

de Kievit, TR, Iglewski, BH. (2000). Bacterial quorum sensing in pathogenic relationships. Infect Immun, 68, 4839–4849.

de Nys, R, Wright, AD, König, GM, Sticher, O.1993. New halogenated furanones from the marine alga *Delisea pulchra* (cf. fimbriata). Tretrahedron, 49, 11213–11220.

Decho, AW, Norman, RS, Visscher, PT. (2010). Quorum sensing in natural environments: emerging views from microbial mats. Trends Microbiol, 18, 73–80.

Defoirdt, T, Boon, N, Bossier, P. (2010). Can bacteria evolve resistance to quorum sensing disruption? PLoS Pathogens, 6, e1000989.

Defoirdt, T, Boon, N, Sorgeloos, P, Verstraete, W, Bossier, P. (2008). Quorum sensing and quorum quenching in *Vibrio harveyi* lessons learned from in vivo work', The ISME J, 2, 19–26.

Defoirdt, T, Crab, R, Wood, TK, Sorgeloos, P, Verstraete, W, Bossier, P. (2006). Quorum sensing–disrupting brominated furanones protect the gnotobiotic brine shrimp *Artemia franciscana* from pathogenic *Vibrio harveyi*, *Vibrio campbellii* and *Vibrio parahaemolyticus* isolates. Appl Environ Microbiol, 72, 6419–6423.

Delalande, L, Faure, D, Raffoux, A, Uroz, S, D'Angelo–Picard, C, Elasri, M, Carlier, A, Berruyer, R, Petit, A, Williams, P, Dessaux, Y. (2005). N-hexanoyl-L-homoserine lactone, a mediator of bacterial quorum–sensing regulation, exhibits plant-dependent stability and may be inactivated by germinating *Lotus corniculatus* seedlings. FEMS Microbiol Ecol, 52, 13–20.

Déziel, E, Gopalan, SS, Tampakaki, AP, Lépine, F, Padfield, KE, Saucier, M, Xiao, G, Rahme, LG. (2005). The contribution of MvfR to *Pseudomonas aeruginosa* pathogenesis and quorum sensing circuitry regulation: multiple quorum sensing–regulated genes are modulated without affecting *lasRI*, *rhlRI* or the production of *N*-acyl-L-homoserine lactones. Mol Microbiol, 55, 998–1014.

Dhillon, NK, Sharma, S, Khuller, GK. (2003). Signaling through protein kinases and transcriptional regulators in *Candida albicans.* Critical Rev Microbiol, 29, 259–275.

Diggle, SP, Griffin, AS, Campbell, GS, West, SA. (2007). Cooperation and conflict in quorumsensing bacterial populations. Nature, 450, 411–414.

Dobretsov, S, Dahms, H-U, YiLi, H, Wahl, ML, Qian, P-Y. (2007). The effect of quorum-sensing blockers on the formation of marine microbial communities and larval attachment. FEMS Microbiol Ecol, 60, 177–188.

Dong, YH, Zhang, LH. (2005). Quorum sensing and quorum-quenching enzymes. J Microbiol, 43, 101–109.

Dong, YH, Gusti, AR, Zhang, Q, Xu, JL, Zhang, LH. (2002). Identification of quorum-quenching N-acyl homoserine lactonases from *Bacillus* species. Appl Environ Microbiol, 68, 1754–1759.

Dong, YH, Wang, LH, Zhang, LH. (2007). Quorum-quenching microbial infections: mechanisms and implications. Phil Trans R Soc Lond B Biol Sci, 362, 1201–1211.

Dong, YH, Wang, LH, Xu, JL, Zhang, HB, Zhang, XF, Zhang, LH. (2001). Quenching quorum–sensing–dependent bacterial infection by an N-acyl homoserine lactonase. Nature, 411, 813–817.

Dong, YH, Xu, JL, Li, XZ, Zhang, LH. (2000). AiiA, an enzyme that inactivates the acylhomoserine lactone quorum-sensing signal and attenuates the virulence of *Erwinia carotovora.* Proc Natl Acad Sci USA, 97, 3526–3531.

Dong, YH, Zhang, XF, Xu, JL, Zhang, LH. (2004). Insecticidal *Bacillus thuringiensis* silences *Erwinia carotovora* virulence by a new form of microbial antagonism, signal interference. Appl Environ Microbiol, 70, 954–960.

Draganov, DI, Stetson, PL, Watson, CE, Billecke, SS, LaDu, BN. (2000). Rabbit serum paraoxonanse 3 (PON3) is a high density lipo–protein–associated lactonase and protects low density lipoprotein against oxidation. J Biol Chem, 275, 33435–33442.

Draganov, DI, Teiber, JF, Speelman, A, Osawa, Y, Sunahara, R, LaDu, BN. (2005). Human paraoxonanses (PON1, PON2 and PON3) are lactonases with overlapping and distinct substrate specificities. J Lipid Res, 46, 1239–1247.

Dunn, MF, Ramirez-Trujillo, JA, Hernandez-Lucas, I. (2009). Major roles of isocitrate lyase and malate synthase in bacterial and fungal pathogenesis. Microbiol, 155, 3166–3175.

Dunny, GM. (2007). The peptide pheromone–inducible conjugation system of *Enterococcus faecalis* plasmid pCF10: cell–cell signaling, gene transfer, complexity and evolution. Phil Trans R Soc Lond B Biol Sci, 362, 1185–1193.

Dunny, GM, Brickman, TJ, Dwarkin, M. (2008). Multicellular behavior in bacteria: communication, cooperation, competition and cheating. BioEssays, 30, 1–3.

Eberl, L, Winson, MK, Sternberg, C, Stewart, GS, Christiansen, G, Chhabra, SR, Bycroft, B, Williams, P, Molin, S, Givskov, M 1996. Involvement of N–acyl–L–hormoserine lactone autoinducers in controlling the multicellular behaviour of *Serratia liquefaciens.* Mol Microbiol, 20, 127–136.

Eckert, R, He, J, Yarbrough, DK, Qi, F,erson, MH, Shi, W. (2006). Targeted killing of *Streptococcus mutans* by a pheromone–guided "Smart" antimicrobial peptide. Antimicrob Agents Chemother, 50, 3651–3657.

Ferrer-Miralles, N, Domingo-Espín, J, Corchero, JL, Vázquez, E, Villaverde, A. (2009). Microbial factories for recombinant pharmaceuticals. Microb Cell Fact, *8, 17.*

Flagan, S, Ching, W–K, Leadbetter, JR. (2003). Arthrobacter strain VAI–A utilizes acyl–homoserine lactone inactivation products

and stimulates quorum signal biodegradation by *Variovorax paradoxus*. Appl Environ Microbiol, 69, 909–916.
Flannery, MC. (2006). Think small, The Am. Biol. Teacher 68, 499–502.
Flavier, AB, Ganova-Raeva, LM, Schell, MA, Denny, TP 1997. Hierarchical autoinduction in *Ralstonia solanacearum*: control of acyl–homoserine lactone production by a novel autoregulatory system responsive to 3–hydroxypalmitic acid methyl ester. J Bacteriol, 179, 7089–7097.
Fray, RG. (2002). Altering plant-microbe interaction through artificially manipulating bacterial quorum sensing. Ann Bot, 89, 245–253.
Fray, RG, Throup, JP, Daykin, M, Wallace, A, Williams, P, Stewart, GS, Grierson, D. (1999). Plants genetically modified to produce N-acylhomoserine lactones communicate with bacteria. Nat Biotechnol, 17, 1017–1020.
Frezza, M, Soulere, L, Deshayes, C, Reverchon, S, Guiliani, N, Jerez, C, Queneau, Y, Doutheau, A. (2008). Synthetic homoserine lactone-derived sulfonylureas as inhibitors of *Vibrio fischeri* quorum sensing regulator. Bioorg Med Chem 16, 3550–3556.
Fuqua, C. (2006). The QscR Quorum-sensing regulon of *Pseudomonas aeruginosa*: an orphan claims its identity. J Bacteriol, 188, 3169–3171.
Fuqua, C, Greenberg, EP. (1998). Self perception in bacteria: quorum sensing with acylated homoserine lactones. Curr Opin Microbiol, 1, 183–189.
Fuqua, C, Parsek, MR, Greenberg, EP. (2001). Regulation of gene expression by cell–to–cell communication: acyl–homoserine lactone quorum sensing. Annu Rev Genet, 35, 439–468.
Fuqua, WC, Winans, SC, Greenberg, EP. (1994). Quorum sensing in bacteria: the LuxR–LuxI family of cell density–responsive transcriptional regulators. J Bacteriol, 176, 269–275.
Gao, M, Teplitski, M, Robinson, JB, Bauer, WD. (2003). Production of substances by *Medicago truncatula* that affect bacterial quorum sensing. Mol Plant Microbe Interact, 16, 827–834.
Gauthier, A, Robertson, ML, Lowden, M, Ibarra, JA, Puente, JL, Finlay, BB. (2005). Transcriptional inhibitor of virulence factors in enteropathogenic *Escherichia coli*. Antimicrob Agents Chemother, 49, 4101–4109.
Geisinger, E, George, EA, Muir, TW, Novick, RP. (2008). Identification of ligand specificity determinants in AgrC, the *Staphylococcus aureus* quorum–sensing receptor. J Biol Chem, 283, 8930–8938.
Geske, GD, O'Neill, JC, Blackwell, HE. (2007). *N*–phenylacetanoyl–Lhomoserine lactones can strongly antagonize or supertagonize quorum sensing in *Vibrio fischeri*. ACS Chem Biol, 2, 315–319.
Ghaffari, A, Miller, CC, McMullin, B, Ghahary, A. (2006). Potential application of gaseous nitric oxide as a topical antimicrobial agent. Nitric Oxide, 14, 21–29.
Givskov, M, de Nys, R, Manefield, M, Gram, L, Maximilien, R, Eberl, L, Molin, S, Steinberg, PD, Kjelleberg, S 1996. Eukaryotic interference with homoserine lactone–mediated prokaryotic signaling. J Bacteriol, 178, 6618–6622.
Givskov, M, Eberl, L, Molin, S 1997. Control of exoenzyme production, motility and cell differentiation in *Serratia liquefaciens*. FEMS Microbiol Lett, 148, 115–122.
González, JE, Marketon, MM. (2003). Quorum sensing in nitrogen–fixing rhizobia. Microbiol, Mol Biol Rev, 67, 574–592.
Gov, Y, Bitler, A, Dell'Acqua, G, Torres, JV, Balaban, N. (2001). RNAIII inhibiting peptide (RIP), a global inhibitor of *Staphylococcus aureus* pathogenesis: structure and function analysis. Peptides, 22, 1609–1620.
Hakenbeck, R, Stock, JB 1996. Analysis of two–component signal transduction systems involved in transcriptional regulation. Methods Enzymol, 273, 281–300.
Harraghy, N, Kerdudou, S, Herrmann, M. (2007). Quorum–sensing systems in *Staphylococci* as therapeutic targets. Anal Bioanal Chem 387, 437–444.
Hassett, DJ, Sutton MD, Schurr, MJ, Herr AB, Caldwell, CC, Matu, JO. (2009). *Pseudomonas aeruginosa* hypoxic or anaerobic biofilm infections within cystic fibrosis airways. Trends Microbiol, 17, 130–138.
Hastings, JW. (2004). Bacterial quorum–sensing signals are inactivated by mammalian cells. Proc Natl Acad Sci USA, 101, 3993–3994.
Hazan, R, Engelberg–Kulka, R. (2004). *Escherichia coli* mazEF–mediated cell death as a defense mechanism that inhibits the spread of phage P1. Mol Genet Genomics, 272, 227–234.
Henke, JM, Bassler, BL. (2004). Three parallel quorum–sensing systems regulate gene expression in *Vibrio harveyi*. J Bacteriol, 186, 6902–6914.
Hentzer M, Riedel K, Rasmussen TB, Heydorn, A,ersen, JB, Parsek, MR, Rice, SA, Eberl, L, Molin, S, Høiby, N, Kjelleberg, S, Givskov, M. (2002). Inhibition of quorum sensing in *Pseudomonas aeruginosa* biofilm bacteria by a halogenated furanone compound. Microbiol, 148, 87–102.
Hentzer, M, Givskov, M. (2003). Pharmacological inhibition of quorum sensing for the treatment of chronic bacterial infections. J Clin Invest, 112, 1300–1307.
Hentzer, M, Wu, H,ersen, JB, Riedel, K, Rasmussen, TB, Bagge, N, Kumar, N, Schembri, MA, Song, Z, Kristoffersen, P, Manefield, M, Costerton, JW, Molin, S, Eberl, L, Steinberg, P, Kjelleberg, S, Høiby, N, Givskov, M. (2003). Attenuation of *Pseudomonas aeruginosa* virulence by quorum sensing inhibitors. EMBO J, 22, 3803–3815.
Hetrick, EM, Shin, JH, Paul, HS, Schoenfisch, MH. (2009). Anti–biofilm efficacy of nitric oxide–releasing silica nanoparticles. Biomater, 30, 2782–2789.
Hetrick, EM, Shin, JH, Stasko, NA, Johnson, CB, Wespe, DA, Holmuhamedov, E, Schoenfisch, MH. (2008). Bactericidal efficacy of nitric oxide-releasing silica nanoparticles. ACS Nano 2, 235–246.
Hibbing, ME, Fuqua, C, Parsek, MR and Peterson, SB. (2009). Bacterial competition: surviving and thriving in the microbial jungle. Nature Rev Microbiol, 8, 15–25.
Hoang, TT, Schweizer, HP. (1999). Characterization of *Pseudomonas aeruginosa* enoyl–acyl carrier protein reductase (FabI): a target for the antimicrobial triclosan and its role in acylated homoserine lactone synthesis. J Bacteriol, 181, 5489–5497.
Hoang, TT, Sullivan, SA, Cusick, JK, Schweizer, HP. (2002). Beta–ketoacyl acyl carrier protein reductase (FabG) activity of the fatty acid biosynthetic pathway is a determining factor of 3–oxo–homoserine lactone acyl chain lengths. Microbiol, 148, 3849–3856.
Hogan, DA, Vik, A, Kolter, R. (2004). A *Pseudomonas aeruginosa* quorum sensing molecule influences *Candida albicans* morphology. Mol Microbiol, 54, 1212–1223.
Holden, MT, Ram, CS, de Nys, R, Stead, P, Bainton, NJ, Hill, PJ, Manefield, M, Kumar, N, Labatte, M, England, D, Rice, S, Givskov, M, Salmond, GP, Stewart, GS, Bycroft, BW, Kjelleberg, S, Williams, P. (1999). Quorum–sensing cross talk: isolation and chemical characterization of cyclic dipeptides from *Pseudomonas aeruginosa* and other gram-negative bacteria. Mol Microbiol, 33, 1254–1266.
http://www.boingboing.net/2010/06/22/do-quorum-sensing-me.html Do quorum sensing meds work?; http://www.boingboing.net/author/rob-beschizza-1/ Rob Beschizza at 11:38 AM Tuesday, Jun 22, 2010 Date Visited: 19th Nov 2010
Huang, JJ, Han, J–I, Zhang, L–H, Leadbetter, JR. (2003). Utilization of acylhomoserine lactone quorum signals for growth by a soil pseudomonad and *Pseudomonas aeruginosa* PAO1. Appl Environ Microbiol, 69, 5941–5949.
Huang, JJ, Petersen, A, Whiteley, M, Leadbetter, JR. (2006). Identification of QuiP, the product of gene *PA1032*, as the second acyl-homoserine lactone acylase of *Pseudomonas aeruginosa* PAO1. Appl Environ Microbiol, 72, 1190–1197.
Hung, DT, Shakhnovich, EA, Pierson, E, Mekalanos, JJ. (2005). Small-molecule inhibitor of *Vibrio cholerae* virulence and intestinal colonization. Science, 310, 670–674.
Ichimiya, T, Takeoka, K, Hiramatsu, K, Hirai, K, Yamasaki, T, Nasu, M 1996. The influence of azithromycin on the biofilm formation of *Pseudomonas aeruginosa* in vitro. Chemother, 42, 186–191.
Imamura, Y, Yanagihara, K, Mizuta, Y, Seki, M, Ohno, H, Higashiyama, Y, Miyazaki, Y, Tsukamoto, K, Hirakata, Y, Tomono, K, Kadota, J,

Kohno, S. (2004). Azithromycin inhibits MUC5AC production induced by the *Pseudomonas aeruginosa* autoinducer N-(3-Oxododecanoyl) homoserine lactone in NCI-H292 cells. Antimicrob Agents Chemother, 48, 3457–3461.

Ishida, T, Ikeda, T, Takiguchi, N, Kuroda, A, Kato, J, Ohtake, H. (2007). Inhibition of quorum sensing in *Pseudomonas aeruginosa* by *N*acyl cyclopentylamides. Appl Environ Microbiol, 73, 3183–3188.

Ji, GYY, Beavis, R, Novick, RP. 1997. Bacterial interference caused by autoinducing peptide variants. Science, 276, 2027–2030.

Joelsson, A, Liu, Z, Zhu, J. (2006). Genetic and phenotypic diversity of quorum-sensing systems in clinical and environmental isolates of *Vibrio cholerae*. Infect Immun, 74, 1141–1147.

Kalia, VC, Rani, A, Lal, S, Cheema, S, Raut, CP. (2007). Combing databases reveals potential antibiotic producers. Expert Opin Drug Discov, 2, 211–224.

Kang, BR, Lee, JH, Ko, SJ, Lee, YH, Cha, JS, Cho, BH, Kim, YC. (2004). Degradation of acyl-homoserine lactone molecules by *Acinetobacter* sp. strain C1010935-941. Can J Microbiol, 50, 935–941.

Kapadnis, PB, Hall, E; Ramstedt, M, Galloway, WRJD, Welch, M, Spring, DR. (2009). Towards quorum-quenching catalytic antibodies. Chem Commun, 5, 538–540.

Kaplan, HB, Plamam, L 1996. A *Myxococcus xanthus* cell density-sensing system required for multicellular development. FEMS Microbiol Lett, 139, 89–95.

Kaufmann, GF, Park, J, Mee, JM, Ulevitch, RJ, Janda, KD. (2008). The quorum quenching antibody RS2–1G9 protects macrophages from the cytotoxic effects of the *Pseudomonas aeruginosa* quorum sensing signaling molecule *N*-3-oxo-dodecanoylhomoserine lactone. Mol Immunol, 45, 2710–2714.

Kaufmann, GF, Sartorio, R, Lee, SH, Mee, JM, Altobell LJ, 3rd, Kujawa, DP, Jeffries, E, Clapham, B, Meijler, MM, Janda, KD. (2006). Antibody interference with N-acyl homoserine lactone–mediated bacterial quorum sensing. J Am Chem Soc, 128, 2802–2803.

Kaufmann, GF, Sartorio, R, Lee, SH, Rogers, CJ, Meijler, MM, Moss, JA, Clapham, B, Brogan, AP, Dickerson, TJ, Janda, KD. (2005). Revisiting quorum-sensing: Discovery of additional chemical and biological functions for 3-oxo-N-acylhomoserine lactones. Proc Natl Acad Sci USA, 102, 309–314.

Khmel, IA, Metlitskaya, AZ. (2006). Quorum sensing regulation of gene expression: a promising target for drugs against bacterial pathogenicity. Mol Biol, 40, 169–182.

Kiran, MD, Adikesavan, NV, Cirioni, O, Giacometti, A, Silvestri, C, Scalise, G, Ghiselli, R, Saba, V, Orlando, F, Shoham, M, Balaban, N. (2008). Discovery of a quorum-sensing inhibitor of drug-resistant Staphylococcal infections by structure-based virtual screening. Mol Pharmacol, 73, 1578–1586.

Koch, B, Liljefors, T, Persson, T, Nielsen, J, Kjelleberg, S, Givskov, M. (2005). The LuxR receptor: the sites of interaction with quorum sensing signals and inhibitors. Microbiol, 151, 3589–3602.

Koutsoudis, M, Tsaltas, D, Minogue, TD, Von Bodman, SB. (2006). Quorum-sensing regulation governs bacterial adhesion, biofilm development, host colonization in *Pontoea stewartii* subspecies *stewartii*. Proc Natl Acad Sci USA, 103, 5983– 5988.

Kuipers, OP, Beerthuyzen, MM, de Ruyter, PG, Luesink, EJ, de Vos, WM 1995. Autoregulation of nisin biosynthesis in *Lactococcus lactis* by signal transduction. J Biol Chem, 270, 27299–27304.

Lamont, IL, Martin LW. (2003). Identification and characterization of novel pyoverdine synthesis genes in *Pseudomonas aeruginosa*. Microbiol, 149, 833–842.

Larimer, FW, Chain, P, Hauser, H, Lamerdin, J, Malfatti, S, Do, L, Land, ML, Pelletier, DA, Beatty, JT, Lang, AS, Tabita, FR, Gibson, JL, Hanson, TE, Bobst, C, Torres, JL, Peres, C, Harrison, FH, Gibson, J, Harwood, CS. (2004). Complete genome sequence of the metabolically versatile photosynthetic bacterium *Rhodopseudomonas palustris*. Nature Biotechnol, 22, 55–61.

Leadbetter, JR, Greenberg, EP. (2000). Metabolism of acylhomoserine lactone quorum-sensing signals by *Variovorax paradoxus*. J Bacteriol, 182, 6921–6926.

Lee, SJ, Park, SY, Lee, JJ, Yum, DY, Koo, BT, Lee, JK. (2002). Genes encoding the N-acyl homoserine lactone–degrading enzyme are widespread in many subspecies of *Bacillus thuringiensis*. Appl Environ Microbiol, 68, 3919–3924.

Li, L, Guo, L, Lux, R, Eckert, R, Yarbrough, D, He, J,erson, M, Shi, W. (2010). Targeted antimicrobial therapy against *Streptococcus mutans* establishes protective non-cariogenic oral biofilms and reduces subsequent infection. Int J Oral Sci, 2, 66–73.

Lin, YH, Xu, JL, Hu, J, Wang, LH, Ong, SL, Leadbetter, JR, Zhang, LH. (2003). 'Acyl-homoserine lactone acylase from *Ralstonia* strain XJ12B represents a novel and potent class of quorum-quenching enzymes. Mol Microbiol, 47, 849–860.

Liu, D, Lepore, BW, Petsko, GA, Thomas, PW, Stone, EM, Fast, W, Ringe, D. (2005). Three-dimensional structure of the quorum-quenching N-acyl homoserine lactone hydrolase from *Bacillus thuringiensis*. Proc Natl Acad Sci USA, 102, 11882–11887.

Lonn-Stensrud, J, Landin, MA, Benneche, T, Petersen, FC, Scheie, AA. (2009). Furanones, potential agents for preventing *Staphylococcus epidermidis* biofilm infections? J. Antimicrob Chemother, 63, 309–316.

Luo, Z-Q, Farrand, SK. (1999). Signal-dependent DNA binding and functional domains of the quorum-sensing activator TraR as identified by repressor activity. Proc Natl Acad Sci USA, 96, 9009–9014.

Lyczak, JB, Cannon, CL, Pier, GB. (2002). Lung infections associated with cystic fibrosis. Clin Microbiol, Rev, 15, 194–222.

Lyon, GJ, Novick, RP. (2004). Peptide signaling in *Staphylococcus aureus* and other Gram-positive bacteria. Peptides, 25, 1389–1403.

Lyon, GJ, Mayville, P, Muir, TW, Novick, RP. (2000). Rational design of a global inhibitor of the virulence response in *Staphylococcus aureus*, based in part on localization of the site of inhibition to the receptor-histidine kinase, AgrC. Proc Natl Acad Sci USA, 97, 13330–13335.

Mae, A, Montesano, M, Koiv, V, Palva, ET. (2001). Transgenic plants producing the bacterial pheromone N-acylhomoserine lactone exhibit enhanced resistance to the bacterial phytopathogen *Erwinia carotovora*. Mol Plant Microbe Interact, 14, 1035–1042.

Manefield, M, Turner, SL. (2002). Quorum sensing in context: out of molecular biology and into microbial ecology. Microbiology 148, 3762–3764.

Manefield, M, de Nys, R, Kumar, N, Read, R, Givskov, M, Steinberg, P, Kjelleberg, S. (1999). Evidence that halogenated furanones from *Delisea pulchra* inhibit acylated homoserine lactone (AHL)-mediated gene expression by displacing the AHL signal from its receptor protein. Microbiol, 145, 283–291.

Manefield, M, Harris, L, Rice, SA, de Nys, R, Kjelleberg, S. (2000). Inhibition of luminescence and virulence in the black tiger prawn (*Penaeus monodon*) pathogen *Vibrio harveyi* by intercellular signal antagonists. Appl Environ Microbiol, 66, 2079–2084.

Manefield, M, Rasmussen, TB, Henzter, M,ersen, JB, Steinberg, P, Kjelleberg, S, Givskov, M. (2002). Halogenated furanones inhibit quorum sensing through accelerated LuxR turnover. Microbiol, 148, 1119–1127.

Manefield, M, Welch, M, Givskov, M, Salmond, GP, Kjelleberg, S. (2001). Halogenated furanones from the red alga, *Delisea pulchra* inhibit carbapenem antibiotic synthesis and exoenzyme virulence factor production in the phytopathogen *Erwinia carotovora*. FEMS Microbiol Lett, 205, 131–138.

Marketon, MM, Gronquist, MR, Eberhard, A, Gonzalez, JE. (2002). Characterization of the *Sinorhizobium meliloti sinR/sinI* locus and the production of novel AHLs. J Bacteriol, 184, 5686–5695.

Marris, E. 2006, Extreme TB strain threatens HIV victims worldwide. Nature, 443, 131.

Martin, CA, Hoven, AD, Cook, AM. (2008). Therapeutic frontiers: preventing and treating infectious diseases by inhibiting bacterial quorum sensing. Eur J Clin Microbiol, Infect Dis, 27, 635–642.

Mathesius, U, Mulders, S, Gao, M, Teplitski, M, Caetano-Anolles, G, Rolfe, BG, Bauer, WD. (2003). Extensive and specific responses of a eukaryote to bacterial quorum-sensing signals. Proc Natl Acad Sci USA, 100, 1444–1449.

Mattmann, ME, Geske, GD, Worzalla, GA, Chandler, JR, Sappington, KJ, Greenberg, EP, Blackwell, HE. (2008). 'Synthetic ligands that activate and inhibit a quorum-sensing regulator in *Pseudomonas aeruginosa*. Bioorg Med Chem Lett, 18, 3072–3075.

McClean, KH, Winson, MK, Fish, L, Taylor, A, Chhabra, SR, Cámara, M, Daykin, M, Swift, S, Lamb, J, Bycroft, BW, Stewart, GSAB, Williams, P 1997. Quorum sensing and *Chromobacterium violaceum*: exploitation of violacein production and inhibition for the detection of *N*-acylhomoserine lactones. Microbiol, 143, 3703–3711.

Melaiye, A, Sun, Z, Hindi, K, Milsted, A, Ely, D, Reneker, DH, Tessier, CA, Youngs, WJ. (2005). Silver(I)–imidazole cyclophane gem-diol, complexes encapsulated by electrospun tecophilic nanofibers: formation of nanosilver particles and antimicrobial activity. J Am Chem Soc, 127, 2285–2291.

Miller, MB, Skorupski, K, Lenz, DH, Taylor, RK, Bassler, BL. (2002). Parallel quorum sensing systems converge to regulate virulence in *Vibrio cholerae*. Cell, 110, 303–314.

Miyairi, S, Tateda, K, Fuse, ET, Ueda, C, Saito, H, Takabatake, T, Ishii, Y, Horikawa, M, Ishiguro, M, Standiford, TJ, Yamaguchi, K. (2006). Immunization with 3-oxododecanoyl-L-homoserine lactone–protein conjugate protects mice from lethal *Pseudomonas aeruginosa* lung infection. J Med Microbiol, 55, 1381–1387.

Mizukane, R, Hirakata, Y, Kaku, M, Ishii, Y, Furuya, N, Ishida, K, Koga, H, Kohno, S, Yamaguchi, K 1994. Comparative *in vitro* exoenzyme-suppressing activities of azithromycin and other macrolide antibiotics against *Pseudomonas aeruginosa*. Antimicrob Agents Chemother, 38, 528–533.

Mok, KC, Wingreen, NS and Bassler, BL. (2003). *Vibrio harveyi* quorum sensing: a coincidence detector for two autoinducers controls gene expression. EMBO J, 22, 870–881.

Molina, L, Constantinescu, F, Michel, L, Reimmann, C, Duffy, B, Defago, G. (2003). Degradation of pathogen quorum-sensing molecules by soil bacteria: a preventive and curative biological control mechanism. FEMS Microbiol Ecol, 45, 71–81.

Molinari, G, Guzmán, C, Pesce, A, Shchito, G 1993. Inhibition of *Pseudomonas aeruginosa* virulence factors by subinhibitory concentrations of azithromycin and other macrolide antibiotics. J Antimicrob Chemother, 31, 681–688.

Morohoshi T, Ebata A, Nakazawa S, Kato N, Ikeda, T. (2005). N-acyl homoserine lactone–producing or –degrading bacteria isolated from the intestinal microbial flora of Ayu fish (*Plecoglossus altivelis*). Microb Environ, 20, 264–268.

Nakayama, J, Uemura, Y, Nishiguchi, K, Norit, Y, Igarashi, Y, Sonomoto, K. (2009). Ambuic acid inhibits the biosynthesis of cyclic peptide quormones in gram–positive bacteria. Antimicrob Agents Chemother, 53, 580–586.

Nalca, Y, Jansch, L, Bredenbruch, F, Geffers, R, Buer, J, Haussler, S. (2006). Quorum–sensing antagonistic activities of azithromycin in *Pseudomonas aeruginosa* PAO1: a global approach. Antimicrob Agents Chemother, 50, 1680–1688.

Nealson, KH, Platt, T, Hastings, JW 1970. Cellular control of the synthesis and activity of the bacterial luminescent system. J Bacteriol, 104, 313–322.

Newton, JA, Fray, RG. (2004). Integration of environmental and host–derived signals with quorum sensing during plant–microbe interactions. Cell Microbiol, 6, 213–224.

Ng, CJ, Shih, DM, Hama, SY, Villa, N, Navab, M, Reddy, ST. (2005). The paraoxonase gene family and atherosclerosis. Free Radical Biol Med, 38, 153–163.

Njoroge, J, Sperandio, V. (2009). Jamming bacterial communication: New approaches for the treatment of infectious diseases. EMBO Mol Med, 1, 201–210.

Olsen, JA, Severinsen, R, Rasmussen, TB, Hentzer, M, Givskov, M, Nielsen, J. (2002). Synthesis of new 3– and 4–substituted analogues of acyl homoserine lactone quorum sensing autoinducers. Bioorg Med Chem Lett, 12, 325–328.

Opal, SM. (2007). Communal living by bacteria and the pathogenesis of urinary tract infections. PLoS Medicine, 4, e349.

Otto, M. (2004). Quorum–sensing control in *Staphylococci*– a target for antimicrobial drug therapy? FEMS Microbiol Lett, 241, 135–141.

Otto, M, Süssmuth, R, Jung, G, Götz, F. (1998). Structure of the pheromone peptide of the *Staphylococcus epidermidis agr* system. FEBS Lett, 424, 89–94.

Park, SY, Hwang, BJ, Shin, MH, Kim, JA, Kim, HK, Lee, JK. (2006). N-acyl homoserine lactone producing *Rhodococcus* s with different AHL-degrading activities. FEMS Microbiol Lett, 261, 102–108.

Park, SY, Kang, HO, Jang, HS, Lee, JK, Koo, BT, Yum, DY. (2005). Identification of extracellular *N*–acylhomoserine lactone acylase from a *Streptomyces* sp. and its application to quorum quenching. Appl Environ Microbiol, 71, 2632–2641.

Park, SY, Lee, SJ, Oh, TK, Oh, JW, Koo, BT, Yum, DY, Lee, JK. (2003). AhlD, an N–acylhomoserine lactonase in *Arthrobacter* sp., predicted homologues in other bacteria. Microbiol, 149, 1541–1550.

Parsek, MR, Greenberg, EP. (2000). Acyl-homoserine lactone quorum sensing in gram-negative bacteria: a signaling mechanism involved in associations with higher organisms. Proc Natl Acad Sci USA, 97, 8789–8793.

Parsek, MR, Val, DL, Hanzelka, BL, Cronan JE, Jr, Greenberg, EP. (1999). Acyl homoserine–lactone quorum–sensing signal generation. Proc Natl Acad Sci USA, 96, 4360–4365.

Patriquin, GM, Banin, E, Gilmour, C, Tuchman, R, Greenberg, EP, Poole, K. (2008). Influence of quorum sensing and iron on twitching motility and biofilm formation in *Pseudomonas aeruginosa*. J Bacteriol, 190, 662–671.

Payne, DJ, Gwynn, MN, Holmes, DJ, Pompliano, DL. (2007). Drugs for bad bugs: confronting the challenges of antibacterial discovery. Nat Rev Drug Discov, 6, 29–40.

Perego, M, Hoch, JA 1996. Cell-cell communication regulates the effects of protein aspartate phosphatases on the phosphorelay controlling development in *Bacillus subtilis*. Proc Natl Acad Sci USA, 93, 1549–1553.

Persson, T, Hansen, TH, Rasmussen, TB, Skindersoe, GE, Givskov, M, Nielsen, KJ. (2005). Rational design and synthesis of new quorum-sensing inhibitors derived from acylated homoserine lactones and natural products from garlic. Org Biomol Chem, 3, 253–262.

Pesci, EC, Milbank, JBJ, Pearson, JP, McKnight, S, Kende, AS, Greenberg, EP, Iglewski, BH. (1999). Quinolone signalling in the cell-to-cell communication system of *Pseudomonas aeruginosa*. Proc Natl Acad Sci USA, 96, 11229–11234.

Peters, L, König, GM, Wright, AD, Pukall, R, Stackebrandt, E, Eberl, L, Riedel, K. (2003). Secondary metabolites of *Flustra foliacea* and their influence on bacteria. Appl Environ Microbiol, 69, 3469–3475.

Petersen FC, Pecharki D, Scheie, AA. (2004). Biofilm mode of growth of *Streptococcus intermedius* favored by a competence–stimulating signaling peptide. J Bacteriol, 186, 6327–6331.

Porwal, S, Lal, S, Cheema, S, Kalia, VC. (2009). Phylogeny in aid of the present and novel microbial lineages: Diversity in *Bacillus*. PLoS ONE, 4, e4438.

Purohit, HJ, Cheema, S, Lal, S, Raut, CP, Kalia VC. (2007). In search of drug targets for *Mycobacterium tuberculosis.* Infect Disord Drug Targets, 7, 245–250.

Qazi, S, Middleton, B, Muharram, SH, Cockayne, A, Hill, P, O'Shea, P, Chhabra, SR, Cámara, M, Williams, P. (2006). '*N*–Acylhomoserine lactones antagonize virulence gene expression and quorum sensing in *Staphylococcus aureus*. Infect Immun, 74, 910–919.

Rahme, LG, Ausubel, FM, Cao, H, Drenkard, E, Goumnerov, BC, Lau, GW, Mahajan–Miklos, S, Plotnikova, J, Tan, M–W, Tsongalis, J, Walendziewicz, CL, Tompkins, RG. (2000). Plants and animals share functionally common bacterial virulence factors. Proc Natl Acad Sci USA, 97, 8815–8821.

Raina, S, De Vizio, D, Odell, M, Clements, M, Vanhulle, S, Keshavarz, T. (2009). Microbial quorum sensing: a tool or a target for antimicrobial therapy? Biotechnol, Appl Biochem, 54, 65–84.

Rasch, M, Buch, C, Austin, B, Slierendrecht, WJ, Ekmann, KS, Larsen, JL, Johansen, C, Riedel, K, Eberl, L, Givskov, M, Gram, L. (2004). An

inhibitor of bacterial quorum sensing reduces mortalities caused by vibriosis in rainbow trout (*Oncorhynchus mykiss*, Walbaum). Syst Appl Microbiol, 27, 350–359.

Rasko, DA, Moreira, CG, Li de, R, Reading, NC, Ritchie, JM, Waldor, MK, Williams, N, Taussig, R, Wei, S, Roth, M, Hughes, DT, Huntley, JF, Fina, MW, Falck, JR, Sperandio, V. (2008). Targeting QseC signaling and virulence for antibiotic development. Science, 321, 1078–1080.

Rasko, DA, Moreira, CG, Li de, R, Reading, NC, Ritchie, JM, Waldor, MK, Williams, N, Taussig, R, Wei, S, Roth, M, Hughes, DT, Huntley, JF, Fina, MW, Falck, JR, Sperandio, V. (2008). Targeting QseC signaling and virulence for antibiotic development. Science, 321, 1078–1080.

Rasmussen, TB, Givskov, M 2006a. Quorum-sensing inhibitors as anti–pathogenic drugs. Int J Med Microbiol, 296, 149–161.

Rasmussen, TB, Givskov, M 2006b. Quorum-sensing inhibitors: a bargain of effects. Microbiol, 152, 895–904.

Rasmussen, TB, Bjarnsholt, T, Skindersoe, ME, Hentzer, M, Kristoffersen, P, Köte, M, Nielsen, J, Eberl, L, Givskov, M 2005a. Screening for quorum-sensing inhibitors (QSI) by use of a novel genetic system, the QSI selector. J Bacteriol, 187, 1799–1814.

Rasmussen, TB, Manefield, M,ersen, JB, Eberl, L, Anthoni, U, Christophersen, C, Steinberg, P, Kjelleberg, S, Givskov, M. (2000). How *Delisea pulchra* furanones affect quorum sensing and swarming motility in *Serratia liquefaciens* MG1. Microbiol, 146, 3237–3244.

Rasmussen, TB, Skindersoe, ME, Bjarnsholt, T, Phipps, RK, Christensen, KB, Jensen, PO,ersen, JB, Koch, B, Larsen, TO, Hentzer, M, Eberl, L, Hoiby, N, Givskov, M. 2005b. Identity and effects of quorum–sensing inhibitors produced by *Penicillium* species. Microbiol, 151, 1325–1340.

Reimmann, C, Ginet, N, Michel, L, Keel, C, Michaux, P, Krishnapillai, V, Zala, M, Heurlier, K, Triandafillu, K, Harms, H, Defago, G, Haas, D. (2002). Genetically programmed autoinducer destruction reduces virulence gene expression and swarming motility in *Pseudomonas aeruginosa* PAO1. Microbiol, 148, 923–932.

Ren, D, Bedzyk, LA, Ye, RW, Thomas, SM, Wood, TK. (2004). Differential gene expression shows natural brominated furanones interfere with the autoinducer-2 bacterial signaling system of *Escherichia coli*. Biotechnol, Bioeng, 88, 630–642.

Ren, D, Sims, J, Wood, TK. (2001). Inhibition of biofilm formation and swarming of *Escherichia coli* by (5Z)-4-bromo-5-(bromomethylene)-3-butyl-2(5H)-furanone. Environ Microbiol, 3, 731–736.

Ren, D, Sims, J, Wood, TK. (2002). Inhibition of biofilm formation and swarming of *Bacillus subtilis* by (5Z)-4-bromo-5-(bromomethylene)-3-butyl-2(5H)-furanone. Lett Appl Microbiol, 34, 293–299.

Resch, A, Rosenstein, R, Nerz, C, Gotz, F. (2005). Differential gene expression profiling of *Staphylococcus aureus* cultivated under biofilm and planktonic conditionsv. Appl Environ Microbiol, 71, 2663–2676.

Riaz, K, Elmerich C, Moreira D, Raffoux A, Dessaux Y, Faure, D. (2008). A metagenomic analysis of soil bacteria extends the diversity of quorum–quenching lactonases. Environ Microbiol, 10, 560–570.

Romero, M, Diggle, SP, Heeb, S, Cámara, C, Otero, A. (2008). Quorum quenching activity in *Anabaena* sp. PCC7120: identification of AiiC, a novel AHL–acylase. FEMS Microbiol Letts, 280, 73–80.

Roy, V, Fernandes, R, Tsao, C-Y, Bentley, WE. (2009). Cross species quorum quenching using a native AI–2 processing enzyme. ACS Chem Biol, 5, 223–232.

Ryan, RP, Dow, JM. (2008). Diffusible signals and interspecies communication in bacteria. Microbiol, 154, 1845–1858.

Saiman, L, Marshall, BC, Saiman, L, Marshall, BC, Mayer–Hamblett, N, Burns, JL, Quittner, AL, Cibene, DA, Coquillette, S, Fieberg, AY, Accurso, FJ, Campbell PW, 3rd, Macrolide Study Group. (2003). Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*: a randomized controlled trial. JAMA, 290, 1749–1756.

Schaefer, AL, Greenberg, EP, Oliver, CM, Oda, Y, Huang, JJ, Bittan–Banin, G, Peres, CM, Schmidt, S, Juhaszova, K, Sufrin, JR, Harwood, CS. (2008). A new class of homoserine lactone quorum–sensing signals. Nature, 454, 595–599.

Schaefer, AL, Val, DL, Hanzelka, BL, Cronan Jr., JE, Greenberg, EP. 1996. Generation of cell-to-cell signals in quorum–sensing: Acyl homoserine lactone synthase activity of a purified *Vibrio fischeri* LuxI protein. Proc Natl Acad Sci USA, 93, 9505–9509.

Schauder, S, Bassler, BL. (2001). The languages of bacteria. Genes and Dev, 15, 1468–1480.

Schertzer, JW, Boulette, ML, Whiteley, M. (2009). More than a signal: non–signaling properties of quorum sensing molecules. Trends Microbiol, 17, 189–195.

Schuster, M, Greenberg, EP. (2007). Early activation of quorum sensing in *Pseudomonas aeruginosa* reveals the architecture of a complex regulon. BMC Genomics, 8, 287.

Shen, G, Rajan, R, Zhu, J, Bell, CE, Pei, D. (2006). Design and synthesis of substrate and intermediate analogue inhibitors of S-ribosylhomocysteinase. J Med Chem, 49, 3003–3011.

Sio, CF, Otten, LG, Cool, RH, Diggle, SP, Braun, PG, Bos, R, Daykin, M, Cámara, M, Williams, P, Quax, WJ. (2006). Quorum Quenching by an *N*-Acyl-Homoserine lactone acylase from *Pseudomonas aeruginosa* PAO1. Infect Immun, 74, 1673–1682.

Smith, KM, Bu, Y, Suga, H. 2003a. Induction and inhibition of *Pseudomonas aeruginosa* quorum sensing by synthetic autoinducer analogs. Chem Biol, 10, 81–89.

Smith, KM, Bu, Y, Suga, H. 2003b. Library screening for synthetic agonists and antagonists of a *Pseudomonas aeruginosa* autoinducer. Chem Biol, 10, 563–571.

Soberón–Chávez, G, Aguirre-Ramírez, M, Ordóñez, L. (2005). Is *Pseudomonas aeruginosa* only "Sensing quorum"? Critical Rev Microbiol, 31, 171–182.

Sofer, D, Gilboa–Garber, N, Beiz, A, Garber, NC. (1999). 'Subinhibitory' erythromycin represses production of *Pseudomonas aeruginosa* lectins, autoinducer and virulence factors. Chemother, 45, 335–341.

Solomon, JM, Magnuson, R, Srivastava, A, Grossman, AD. 1995. Convergent sensing pathways mediate response to two extracellular competence factors in *Bacillus subtilis*. Genes and Dev, 9, 547–558.

Somers, E, Vanderleyden, J, Srinivasan M. (2004). Rhizosphere bacterial signalling: A love parade beneath our feet. Critical Rev Microbiol, 30, 205–240.

Sperandio, V, Torres, AG, Jarvis, B, Nataro, JP, Kaper, JB. (2003). Bacteria–host communication: The language of hormones. Proc Natl Acad Sci USA, 100, 8951–8956.

Stein, T, Borchert, S, Kiesau, P, Heinzmann, S, Klöss, S, Klein, C, Helfrich, M, Entian, KD. (2002). Dual control of subtilin biosynthesis and immunity in *Bacillus subtilis*. Mol Microbiol, 44, 403–416.

Stephenson, K, Yamaguchi, Y, Hoch, JA. (2000). The mechanism of action of inhibitors of bacterial two–component signal transduction systems. J Biol Chem, 275, 38900–38904.

Stoltz, DA, Ozer, EA, Taft, PJ, Barry, M, Liu, L, Kiss, PJ, Moninger, TO, Parsek, MR, Zabner, J. (2008). *Drosophila* are protected from *Pseudomonas aeruginosa* lethality by transgenic expression of paraoxonase–1. J Clin Invest, 118, 3123–3131.

Sundaramurthy, V, Pieters, J. (2007). Interactions of pathogenic mycobacteria with host macrophages. Microbes Infect, 9, 1671–1679.

Suntharalingam, P, Cvitkovitch, DG. (2005). Quorum sensing in streptococcal biofilm formation. Trends Microbiol, 13, 3–6.

Swift, S, Lynch, MJ, Fish, L, Kirke, DF, Tomas, JM, Stewart, GSAB, Williams, P. (1999). Quorum sensing-dependent regulation and blockade of exoprotease production in *Aeromonas hydrophila*. Infect Immun, 67, 5192–5199.

Taga, M, Bassler, BL. (2003). Chemical communication among bacteria. Proc Natl Acad Sci USA, 100, 14549–14554.

Tateda, K, Comte, R, Pechere, J–C, Köhler, T, Yamaguchi, K, van Delden, C. (2001). Azithromycin inhibits quorum sensing in *Pseudomonas aeruginosa*. Antimicrob Agents Chemother, 45:1930–1933.

Tateda, K, Ishii, Y, Horikawa, M, Matsumoto, T, Miyairi, S, Pechere, JC, Standiford, TJ, Ishiguro, M, Yamaguchi, K. (2003). The *Pseudomonas aeruginosa*. autoinducer N-3-oxododecanoyl homoserine lactone accelerates apoptosis in macrophages and neutrophils. Infect Immun, 71, 5785–5793.

Teplitski, M, Chen, H, Rajamani, S, Gao, M, Merighi, M, Sayre, RT, Robinson, JB, Rolfe, BG, Bauer, WD. (2004). *Chlamydomonas reinhardtii* secretes compounds that mimic bacterial signals and interfere with quorum sensing regulation in bacteria. Plant Physiol, 134, 137–146.

Teplitski, M, Robinson, JB, Bauer, WD. (2000). Plants secrete substances that mimic bacterial N–acyl homoserine lactone signal activities and affect population density-dependent behaviors in associated bacteria. Mol Plant Microbe Interact, 13, 637–648.

Thomas, PW, Stone, EM, Costello, AL, Tierney, DL, Fast, W. (2005). The quorum-quenching lactonase from *Bacillus thuringiensis* is a metalloprotein. Biochem, 44, 7559–7569.

Turovskiy, Y, Kashtanov, D, Paskhover, B, Chikindas, ML. (2007). Quorum sensing: fact, fiction, everything in between. Adv Appl Microbiol, 62, 191–234.

Ueda, A, Wood, TK. (2009). Connecting quorum sensing, c-di-GMP, Pel polysaccharide, biofilm formation in *Pseudomonas aeruginosa* through tyrosine phosphatase TpbA (PA3885). PLoS Pathogens 5, e1000483

Ulrich, RL. (2004). Quorum quenching: enzymatic disruption of N-acylhomoserine lactone-mediated bacterial communication in *Burkholderia thailandensis*. Appl Environ Microbiol, 70, 6173–6180.

Uroz, S, Heinon, J. (2008). Degradation of n-acyl homoserine lactone quorum sensing signal molecules by forest root associated fungi. FEMS Microbiol Ecol, 65, 271–278.

Uroz, S, Chhabra, SR, Cámara, M, Wiliams, P, Oger, PM and Dessaux, Y. (2005). N-Acylhomoserine lactone quorum–sensing molecules are modified and degraded by *Rhodococcus erythropolis* W2 by both amidolytic and novel oxidoreductase activities. Microbiol, 151, 3313–3322.

Uroz, S, DAngelo–Picard, C, Carlier, A, Elasri, M, Sicot, C, Petit, A, Oger, P, Faure, D, Dessaux, Y. (2003). Novel bacteria degrading N-acylhomoserine lactones and their use as quenchers of quorum-sensing-regulated functions of plant-pathogenic bacteria. Microbiol, 149, 1981–1989.

Uroz, S, Dessaux, Y, Oger, P. (2009). Quorum sensing and quorum quenching: The Yin and Yang of bacterial communication. ChemBiochem, 10, 205–216

Uroz, S, Oger, P, Chhabra, SR, Cámara, M, Williams, P, Dessaux, Y. (2007). N-acyl-homoserine lactones are degraded via an amidolytic activity in *Comamonas* sp. strain D1. Arch Microbiol, 187, 249–256.

Uroz, S, Oger, PM, Chapelle, E, Adeline, MT, Faure, D, Dessaux, Y. (2008). A *Rhodococcus qsdA*-encoded enzyme defines a novel class of large-spectrum quorum-quenching lactonases. Appl Environ Microbiol, 74, 1357–1366.

Vandeputte, OM, Kiendrebeogo, M, Rajaonson, S, Diallo, B, Mol, A, Jaziri, ME, Baucher, M. (2010). Identification of catechin as one of the flavonoids from *Combretum albiflorum* bark extract that reduces the production of quorum-sensing-controlled virulence factors in *Pseudomonas aeruginosa* PAO1. Appl Environ Microbiol, 71, 243–253.

von Bodman, SB, Willey, JM, Diggle, SP. (2008). Cell-Cell Communication in bacteria: United we stand. J Biotechnol, 190, 4377–4391.

Vuong, C, Kocianova, S, Yao, Y, Carmody, AB, Otto, M. (2004). Increased colonization of indwelling medical devices by quorum-sensing mutants of *Staphylococcus epidermidis in vivo*. J Infect Dis, 190, 1498–1505.

Vuong, C, Saenz, HL, Gotz, F, Otto, M. (2000). Impact of the agr quorum-sensing system on adherence to polystyrene in *Staphylococcus aureus*. J Infect Dis, 182:1688–1693.

Wagner, VE, Frelinger, JG, Barth, RK, Iglewski, BH. (2006). Quorum sensing: dynamic response of *Pseudomonas aeruginosa* to external signals. Trends Microbiol, 14, 55–58.

Walters, M, Sperandio, V. (2006). Quorum sensing in *Escherichia coli* and *Salmonella*. Int J Med Microbiol, 296, 125–131.

Wang, LH, Weng, LX, Dong, YH, Zhang, LH. (2004). Specificity and enzyme kinetics of the quorum–quenching N-Acyl homoserine lactone lactonase (AHL-lactonase). J Biol Chem, 279, 13645–13651.

Wang, W, Morohoshi, T, Ikeda, T, Chen, L. (2008). Inhibition of Lux quorum-sensing system by synthetic *N*-acyl-L-homoserine lactone analogous. Acta Biochim Biophys Sin, 40, 1023–1028.

Waters, CM, Bassler, BL. (2005). Quorum sensing: cell-to-cell communication in bacteria. Annu Rev Dev Biol, 21, 319–346.

Watson, WT, Minogue, TD, Val, DL, von Bodman, SB, Churchill, ME. (2002). Structural basis and specificity of acyl-homoserine lactone signal production in bacterial quorum sensing. Mol Cell, 9, 685–694.

Wei, JR, Tsai, Y-H, Horng, Y-T, Soo, P-C, Hsieh, S-C, Hsueh, P-R, Horng, J-T, Williams, P, Lai, H-C. (2006). A mobile quorum-sensing system in *Serratia marcescens*. J Bacteriol, 188, 1518–1525.

Williams, P. (2002). Quorum sensing: an emerging target for antibacterial chemotherapy? Expert Opin Ther Targets, 6, 257–274.

Winans, SC, Bassler, BL. (2002). Mob psychology. J Biotechnol, 184, 873–883.

Winzer, K, Hardie, KR, Williams, P. (2002). Bacterial cell-to-cell communication: sorry, cant talk now – gone to lunch! Curr Opin Microbiol, 5, 216–222.

Wisniewski–Dyé, F, Downie, JA. (2002). Quorum-sensing in *Rhizobium*. Antonie Van Leeuwenhoek 81, 397–407.

Wright III, JS, Lyon, GJ, Goerge, EA, Muir, TW, Novick, RP. (2004). Hydrophobic interactions drive ligand – receptor recognition for activation and inhibition of staphylococcal quorum sensing. Proc Natl Acad Sci USA, 101, 16168–16173.

Wright, GD. (2005). The antibiotic resistome: the nexus of chemical and genetic diversity. Nat Rev Microbiol, 5, 175–186.

Wu, H, Song, Z, Hentzer, M,ersen, JB, Molin, S, Givskov, M, Hoiby, N. (2004). Synthetic furanones inhibit quorum-sensing and enhance bacterial clearance in *Pseudomonas aeruginosa* lung infection in mice. J Antimicrob Chemther, 53, 1054–1061.

Xavier, KB, Bassler, BL. (2003). LuxS quorum sensing: more than just a numbers game. Curr Opin Microbiol, 6, 191–197.

Xavier, KB, Bassler, BL. (2005). Regulation of uptake and processing of the quorum–sensing autoinducer AI–2 in *Escherichia coli*. J Biotechnol, 187, 238–248.

Xu, F, Byun, T, Deussen, HJ, Duke, KR, Dussen, HJ. (2003). Degradation of N–acylhomoserine lactones, the bacterial quorum sensing molecules by acylase. J Biotechnol, 101, 89–96.

Yamamoto, T, Kaneko, M, Changchawalit, S, Serichantalergs, O, Ijuin, S, Echeverria, P 1994. Actin accumulation associated with clustered and localized adherence in *Escherichia coli* isolated from patients with diarrhea. Infect Immun, 62, 2917–2929.

Yang, F, Wang, L-H, Wang, J, Dong, Y-H, Hu, JY, Zhang, L-H. (2005). Quorum quenching enzyme activity is widely conserved in sera of mammalian species. FEBS Letts, 579, 3713–3717.

Yang, S, Lopez, CR, Zechiedrich, EL. (2006). Quorum sensing and multi–drug transporters in *Escherichia coli*. Proc Natl Acad Sci USA, 103, 2386–2391.

Yarwood, JM, Schlievert, PM. (2003). Quorum sensing in *Staphylococcus* infections. J Clin Invest, 112, 1620–1625.

Yarwood, JM, Volper, EM, Greenberg, EP. (2005). Delays in *Pseudomonas aeruginosa* quorum–controlled gene expression are conditional. Proc Natl Acad Sci USA, 102, 9008–9013.

Yates, EA, Philipp, B, Buckley, C, Atkinson, S, Chhabra, SR, Sockett, RE, Goldner, M, Dessaux, Y, Cámara, M, Smith, H, Williams, P. (2002). N–Acylhomoserine lactones undergo lactonolysis in a pH–, temperature–, acyl chain length–dependent manner during growth

of *Yersinia pseudotuberculosis* and *Pseudomonas aeruginosa*. Infect Immun, 70, 5635–5646.

Zhang, HB, Wang, C, Zhang, LH. (2004). The quormone degradation system of *Agrobacterium tumefaciens* is regulated by starvation signal and stress alarmone (p)ppGpp. Mol Microbiol, 52, 1389–1401.

Zhang, HB, Wang, LH, Zhang, LH. (2002). Genetic control of quorum–sensing signal turnover in *Agrobacterium tumefaciens*. Proc Natl Acad Sci USA, 99, 4638–4643.

Zhang, L-H.(2003). Quorum quenching and proactive host defense. Trends in Pl Sci 8, 238–244.

Zhang, L-H, Dong, Y-H. (2004). Quorum sensing and signal interference: diverse implications. Mol Microbiol, 53, 1563–1571.

Zhu, J, Winans, SC. (1999). Autoinducer binding by quorum–sensing regulator TraR increases affinity for target promoters in vitro and decreases TraR turnover rates in whole cells. Proc Natl Acad Sci USA, 96, 4832–4837.

Zhu, J, Miller, MB, Vance, RE, Dziejman, M, Bassler, BL, Mekalanos, JJ. (2002). Quorum–sensing regulators control virulence gene expression in *Vibrio cholerae.* Proc Natl Acad Sci USA, 99, 3129–3134.