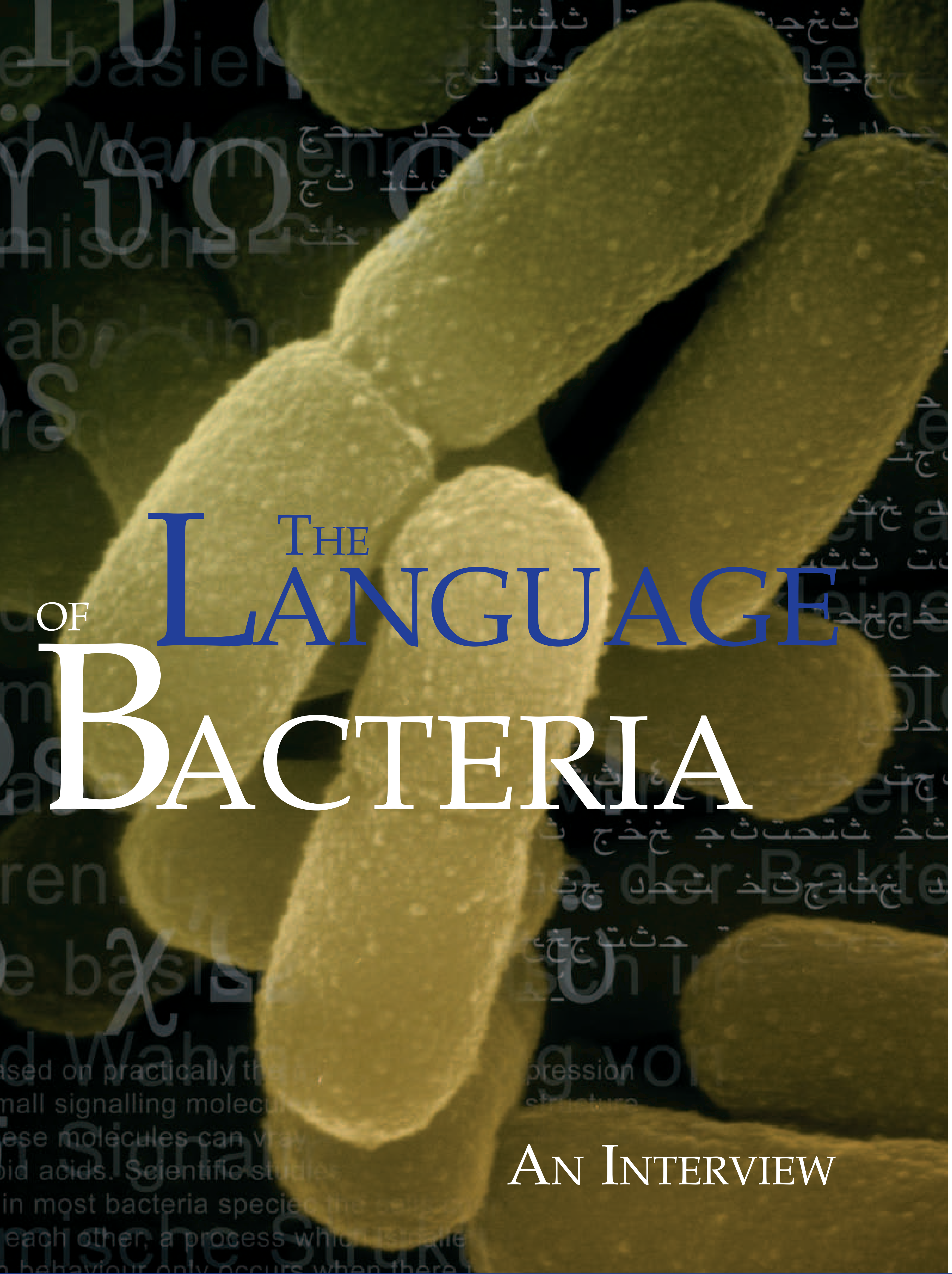


# The Language of Bacteria

## An Interview

The exchange of information is of fundamental importance not only for higher organisms, such as humans. Studies have revealed that even bacteria communicate with each other. It is an important task to decode these microbial messages, since this could lead to the development of a new generation of therapeutics. We have interviewed Prof. Dr. Leo Eberl from the University of Zurich about this topic, one of the leading experts in the area of bacterial communication.

### For the layman, bacteria are very simple organisms with a short lifespan. Why is communication important to them?

For a long time, bacteria were regarded as isolated, unicellular organisms that barely interact with each other. However, in recent years there is increasing insight that most bacteria exist in their natural environment as surface-associated multicellular communities, so-called biofilms. This is of eminent importance, since the physiology of sessile bacteria is fundamentally different from that of free-swimming cells. Of particular importance in the area of medicine is the dramatically increased resistance of biofilms against antibiotics, biocides and host immune responses. It is estimated that about 65% of all infections in the developed world are connected with the establishment of biofilms.

Recent studies have impressively shown that cells of most bacterial species communicate with each other, a process that is known today as "quorum sensing" (QS). It is assumed that particular behavioral patterns only surface if a corresponding number of bacteria is present. The smallest unit that is capable of coordinated action is called quorum. Due to extremely high cell densities found in biofilms, cell-cell communication plays a key role here. For some bacteria is could be demonstrated that QS systems are responsible for the development of normal biofilms.

### How can one imagine such a bacterial language?

The bacterial language is of chemical nature, i.e., it is almost always based on the production and perception of small signal molecules. However, the chemical structure of these molecules is very variable and encompasses short peptides as well as fatty acids. The group of signals with the widest distribution are the N-acyl homoserine lactones (AHL) that have been detected in more than 50 bacterial species. QS systems are involved in the regulation of a multitude of very diverse functions, often in connection with the formation of biofilms or the production of extracellular hydrolytic enzymes and virulence factors. In addition, newest studies have shown that AHL signal molecules are of crucial importance for the interaction of bacteria with their eukaryotic hosts (in symbiotic as well as pathogenic relationships). My research group is exclusively interested in AHL-mediated communication.

Prof. Dr. Leo Eberl

Can you name particularly interesting examples of bacterial communication?

The more data are generated, the more we become aware that bacterial communication affects all aspects of bacterial life. In many cases properties are controlled that are responsible for pathogenic or symbiotic traits (and are therefore immediately connected with the interaction with the host organism).

### How are the chemical messages deciphered in the laboratory?

To demonstrate communication between bacteria in their natural habitat, we have developed specific bacterial biosensors. These contain gene fusions of various AHL-dependent regulatory elements with the reporter gene gfp, which encodes the green fluorescent protein. These biosensors are only activated, i.e., they only fluoresce green, if AHLs are present. By employing theses biosensors it was possible for the first time to detect AHL-mediated communication at

**Bacteria**
Microscopic, mostly unicellular organisms that lack a nucleus

**Sessile**
Organisms are called sessile if they are unable to move about their habitat but are attached to one location. Examples are all plants, corals, etc.

**Cystic fibrosis**
(Mucoviscidosis)
Belongs to the most common innate metabolic diseases (ca. 1 : 2000 newborns in Europe) and is caused by the lack of CFTR (cystic fibrosis transmembrane regulator), a regulatory protein of chloride transport through the cell membrane.

**Signal transduction**
Chain-like biochemical processes that permit the cell to react to external stimuli. This process involves many enzymes and low-molecular signals that transmit the message to the cell nucleus.

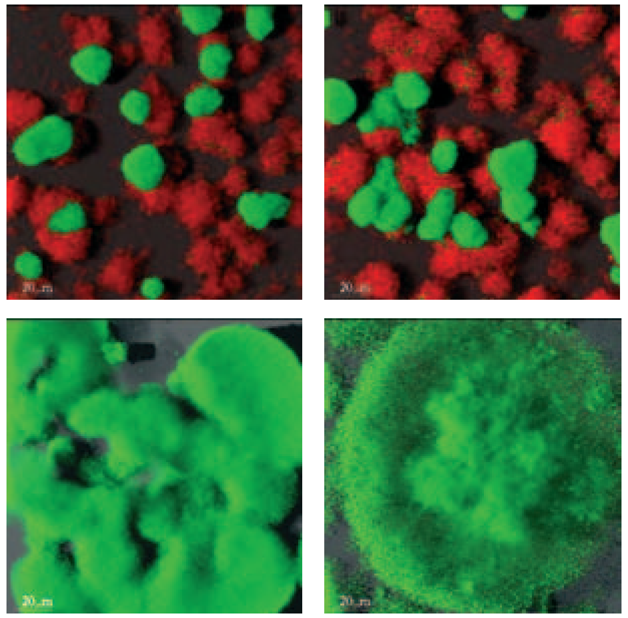
the single-cell level in complex habitats. In this way we could show that Pseudomonas aeruginosa produces AHL molecules in the lung tissue of infected mice and that in plant-associated bacteria AHL molecules are used in interspecies communication at plant roots. These biosensors are also the basis for the development of a high-throughput screening method to identify potential AHL blockers in combinatorial substance libraries and in extracts containing natural products.

## In most habitats, a great diversity of microorganims is present in a very small space. How is miscommunication avoided?

Only preliminary studies exist about this topic. Some bacteria are indeed able to communicate across species boundaries. Interestingly, some bacteria are even able to degrade specific AHL molecules and in this way to disturb communication between potential competitors.

## With a detailed knowledge about bacterial signals, do we have the possibility to specifically disrupt communication and thus combat or prevent infection?

The insight that bacterial communication systems play a central role in regulating the expression of virulence factors renders them attractive targets for the development of new therapeutics. The disruption of the cell-cell signal transduction cascade could be a particularly promising strategy to treat patients with cystic fibrosis. Presently, the inhibition of the AHL receptor protein is probably the most promising strategy to inhibit QS systems. Indeed, we know that some organisms produce substances that specifically interfere with bacterial QS systems. The best-studied examples are secondary metabolites of the marine macoalga Delisea pulchra, which are halogenated furanones that interact with AHL-regulated processes. However, the furanones studied to date are very unstable and highly cytotoxic, which strongly limits their practical utility. A key focus of our present research is therefore the identification of novel quorum sensing blockers that specifically inhibit binding of the AHL molecule to its receptor protein. In collaboration with the biotechnological company 4SC AG, potential QS inhibitor substances are designed on the basis of known protein and modulator structures via computer-aided high-throughput screens (4Scan©). The activity and specificity of candidate substances are subsequently assessed using various biological test systems. The main advantage of these bioactive substances is that they do not inhibit bacterial growth but suppress the expression of pathogenic traits. Since the inhibition of pathogenic properties does not exert a selection pressor, it can be assumed that, unlike with conventional antibiotics, no resistant mutants arise.



Microscopic pictures of biofilms from the pathogenic bacteria *Burkholderia cepacia* (green) and *Pseudomonas aeruginosa* (red)

## Which other important reasons do you see to elucidate the bacterial language?

There are several pragmatic reasons. Some of the functions regulated by communication are of great economic interest, e.g., the generation of important antibacterial agents and fungicides or the production of biotechnologically interesting hydrolytic enzymes. But fascinating strategies also exist in the area of basic research. It is suspected today that bacterial communication in biofilms proceeds in a similar way as hormone-dependent interaction between individual cells in multicellular organisms. The fact that many higher organisms are able to perceive bacterial communication suggests that we are dealing with an archaic language of life.

## What is your impression about the present state of research in the area of bacterial communication, and where do you see the need to catch up?

This is one of the fastest developing areas in microbiology with exponentially increasing numbers of publications. This trend will likely continue, since in more and more microorganisms communication systems are discovered. Unfortunately this area is rarely studied in Germany and is still in its infancy here.

Many thanks, Prof. Eberl, for this interview.

Jörn Piel

### Additional Literature

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### Links on the Web

Science Library der Univerity at Albany
http://library.albany.edu/science/newinsci_quorum_sensing.htm

Quorum sensing, Biofilme & Antibiotikaresistenzen
www2.biologie.uni-halle.de/genet/plant/staff/koebnik/teaching/mabi2005/VL06-Quorum&Antibiotika.pdf