

International Centre for Genetic Engineering and Biotechnology



ARTURO FALASCHI CONFERENCE



28-30 October 2025 | Trieste, ITALY

AREA SCIENCE PARK

Località Padriciano 99
34149 Trieste TS

PROGRAMME



ORGANISERS

Vittorio Venturi (ICGEB Trieste, Italy; UM6P, Ben Guerir, Morocco)
Cristina Bez (ICGEB Trieste, Italy)
Livia Leoni (University Roma3, Italy)
Giordano Rampioni (University Roma3, Italy)
Leo Eberl (University of Zurich, Switzerland)
Miguel Cámara (University of Nottingham, UK)
Pete Greenberg (University of Washington, USA)
Eric Déziel (INRS, Canada)
Martin Welch (University of Cambridge, UK)
Steve Diggie (Georgia Institute of Technology, USA)
Ines Mandić Mulec (University of Ljubljana, Slovenia)

TOPICS

- Intercellular bacterial signaling and viruses
- Intercellular bacterial signaling in biofilms
- Sociomicrobiology and intercellular bacterial signaling
- Phenotypic (gene expression) heterogeneity and intercellular bacterial signaling
- Molecular and biochemical mechanism(s) of intercellular bacterial signalling
- Computational and simulation tools and intercellular bacterial signalling
- Genomics and evolution of intercellular bacterial signaling
- Regulation of intercellular bacterial signaling
- Bacterial inter-species and bacteria-inter/kingdom cell-cell signaling
- Intercellular signaling in host-microbe interactions
- Blocking of intercellular signaling as anti-virulence

<https://www.icgeb.org/cell-cell-communication-in-bacteria-trieste-2025/>

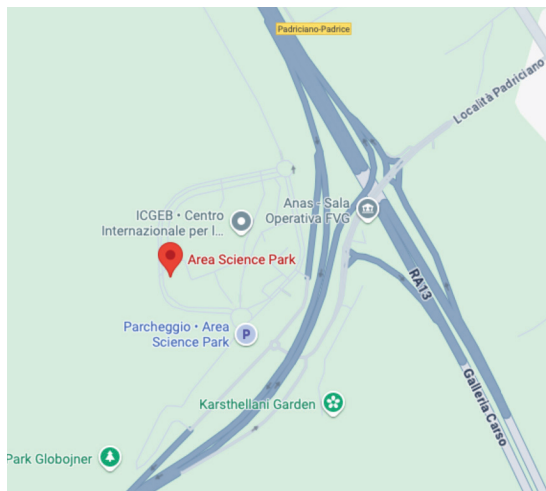
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"Cell-cell communication in bacteria: new insights and future trends"

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General Information



Meeting Location

The Meeting will be held in the Congress Centre of the AREA Science Park, Padriciano, Trieste, where free parking will be available.

Secretariat:

The Registration Desk is in the Congress Centre of the AREA Science Park.

Internet and Wi-Fi access will be available in the Congress Centre.

Your name badge is required for admission to the Meeting - please wear it at all times.

Registration

Registration starts at 13.30 on Tuesday 28th October

Technical Services

The Multimedia Centre is located adjacent to the auditorium, where a technician will be present to provide assistance.

Oral Presentations

Speakers should please load and check their presentations as soon as possible and stick to their allocated time.

Oral presentation abstracts are numbered 1 onwards by page number in the Abstract Book, in order of presentation in the Programme.

Poster Presentations

Poster presentation abstracts are numbered 40 onwards and are printed in alphabetical order, under the surname of the presenting author.

Posters should be displayed for the duration of the meeting and can be put up **during Registration**.

Please remember to take them down **before** the final session

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Please note that a private ICGEB bus will leave
from Savoia Excelsior Palace:

Tuesday, 28 October: **1.00 pm**

Wednesday, 29 October: 8.30 am

Thursday, 30 October: 8.30 am

to take you to the AREA Science Park
where the Meeting will be held
(approx. 20 minutes from the city centre).

You are kindly requested to be prompt.

The bus, due to traffic regulations, cannot wait for late-comers.

The Pick-up point is at the Savoia Excelsior Palace,
Riva del Mandracchio 6

Scan the QR code here below to find
the exact location on Google maps



Alternatively, bus number 51/ departs from Trieste train station (Piazza della Libertà) and goes to the AREA Science Park of Padriciano

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Trieste

What to see in the city

- San Giusto Castle and Cathedral
- Piazza dell'Unità
- Molo Audace and seafront walk
- Grand Canal & Ponterosso
- Miramare Castle
- Old City and jewish ghetto
- Boat trip to Muggia city

Historic caffès

- Caffè degli Specchi, Piazza Unità d'Italia, 7
- Caffè Tommaseo, Piazza Nicolò Tommaseo, 4
- Antico Caffè San Marco, Via Cesare Battisti, 18
- Antico Caffè Torinese, Corso Italia, 2
- Eppinger, Via Dante Alighieri, 2
- Caffè Illy, Via Gioacchino Rossini, 2
- La Bomboniera, Via XXX Ottobre, 3

Restaurants

- Trattoria Da Giovanni, Via S. Lazzaro, 14/b
- Buffet da Pepi, Via della Cassa di Risparmio, 3
- PuRo, Via Torino, 31
- Da Siora Rosa, Piazza Hortis, 3
- Ai Fiori, Piazza Attilio Hortis, 7
- Joia, Riva Tommaso Gulli, 4/a
- Cio' che piace, Via Armando Diaz, 22
- Eataly, Riva Tommaso Gulli, 1

Pizzerias

- Da Pino, Via Ottaviano Augusto, 2B
- Bianco, Via G. Rossini, 8 e Via A. Diaz, 2
- Il Melograno, Via di Cavana, 14
- Assaje, Via Torino, 33
- Caprese, Piazza della Borsa, 15
- Spiller, Riva Nazario Sauro, 14

Bars & Drinks

You will find many, MANY options around the city centre and in Via di Cavana/via Torino, on the "Rive" (Riva Nazario Sauro, Riva Tre Novembre) as well as several "enoteche" (wineries) such as Bischoff, established in 1777, enoteca Hortis, Nanut and Giovinoto, just to name a few.

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Programme

Tuesday 28th October

- 13.00 *Bus to the meeting venue*
- 13.30–14.30 REGISTRATION
1st Floor C1 Building AREA Science Park
- 14.30–14.40 Welcome address by **Vittorio Venturi**, ICGBE, Trieste, Italy and UM6P, Ben Guerir, Morocco

Opening Keynote Lecture

Moderator Miguel Cámara

14.40–15.25	Acylhomoserine Lactone Quorum Sensing: What We Know and What We Want to Know	Peter Greenberg , Washington University, Seattle, USA
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Session 1

Molecular Mechanisms of intercellular bacterial signaling

Moderator Eric Déziel

15.25–15.50	Timing is everything: how <i>Pseudomonas aeruginosa</i> makes and breaks a quorum	Jon Paczkowski , University at Albany, New York, USA
15.50–16.15	LuxR solos mediate host specific inter-kingdom signaling in <i>Photobacterium luminescens</i>	Ralf Heermann , Johannes Gutenberg University Mainz, Germany
16.15–16.30	Accelerated discovery of novel quorum-sensing bypass mutations using inducible hypermutator strains of <i>Pseudomonas aeruginosa</i>	Isabel Askenasy , University of Cambridge, UK
16.30–16.45	LuxR solos as major proteobacterial players of cell-cell signaling in the plant microbiome (LuxSoM)	Cristina Bez , ICGBE Trieste, Italy
16.45–17.00	Regulatory mechanisms of mupirocin biosynthesis in <i>Pseudomonas fluorescens</i> NCIMB 10586	Yuyuan Cai , Shanghai Jiao Tong University, China
17.00–17.20	<i>Coffee break</i>	
17.20–17.35	Calcium dependence and dynamics in mycobacterial cell-cell interaction	Todd Gray , Wadsworth Center, Albany, USA

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17.35-17.50	<i>Pseudomonas aeruginosa</i> quorum sensing during chronic human infection	Morgana Letizia , Georgia Institute of Technology, Atlanta, USA
17.50-18.05	RsaM – not a switch but a built-in modulator of quorum sensing in <i>Pseudomonas fuscovaginae</i>	Nemanja Ristovic , ICGEB Trieste, Italy
18.05-19.30	Poster session 1 – even numbers	
19.35	<i>Bus to the city center – Social event</i>	

Wednesday 29th October

8.30 *Bus to the meeting venue*

Session 2

Ecology and Evolution of intercellular bacterial signaling

Moderator Ralf Heermann

9.00-9.25	Interference competition mechanisms in a bacterial symbiont	Tim Miyashiro , Pennsylvania State University, USA
9.25-9.50	Enterobacterial signalling, antibiotics and morphogen-mediated flotation	George Salmond , University of Cambridge, UK
9.50-10.05	Quorum sensing deficiency enhances salt stress adaptation in <i>Bacillus subtilis</i> through altered gene regulation	Tjasa Danevcic , University of Ljubljana, Slovenia
10.05-10.20	A sea of signals: quorum sensing regulates chitin degradation in marine bacterial communities	Rachel Gregor , University of Toronto, Canada
10.20-10.35	Lineage and microenvironment effects drive heterogeneous quorum sensing activation in <i>Pseudomonas aeruginosa</i> microcolonies	Xiaohe Liu , University of Zürich, Switzerland
10.35-10.50	Quorum sensing plasticity in <i>Pseudomonas aeruginosa</i> : Ecological insights into strains deficient in production of 4-hydroxy-2-alkylquinolines (HAQs)	Mylene Trottier , INRS Centre Armand-Frappier, Laval, Canada
10.50-11.05	Dissecting cyclic lipopeptide Biosynthesis Regulation in Poly-Producing <i>Pseudomonas</i> with and without Quorum Sensing System	Lu Zhou , Ghent University, Belgium
11.05-11.30	<i>Coffee break</i>	

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Session 3

Novel and emerging mechanisms of microbial communication

Moderator Steve Diggle

11.30-11.55	Cell-cell signaling in <i>Haloferax volcanii</i> : how archaea communicate	Mechthild Pohlschroder , University of Pennsylvania, Philadelphia, USA
11.55-12.20	Femtomolar signals and microalgal mating: the chemical ecology of diatom reproduction	George Pohnert , Friedrich Schiller University, Germany
12.20-12.45	Unraveling Mechanisms Behind Coexistence within Microbial Ecosystems	Michael Meijler , Ben-Gurion University of the Negev, Israel
12.45-13.00	Bacterial nanotubes emerge from a membranous organelle to establish an intercellular bridge	Manas Kumar Guria , The Hebrew University of Jerusalem, Israel

13.00-14.30 **Poster session 2** – odd numbers – with lunch

Session 4

Cooperation, competition and communication

Moderator Ines Mandic Mulec

14.30-14.55	Cell surface Hydrophobicity and spatial proximity impact the fitness of quorum sensing cheaters in <i>Pseudomonas aeruginosa</i>	Steve Diggle , School of Biological Sciences at Georgia Tech, Atlanta, USA
14.55-15.20	Predictive microbiome engineering	Lingchong You , Center for Quantitative Biodesign, Duke University, USA
15.20-15.35	The acquisition of additional control over quorum sensing regulation reduces the variability of final cell density	Marco Fondi , University of Florence, Italy
15.35-15.50	<i>P. aeruginosa</i> relies on sensing and communication systems to interact with competing opportunistic human pathogens	Clémentine Laffont , University of Zurich, Switzerland

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15.50-16.05	Modulation of interbacterial interactions by <i>Pseudomonas aeruginosa</i> quorum sensing	Andrew Frando , University of Washington, Seattle, USA
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16.05-16.35 *Coffee break*

Session 5

Signaling in biofilms and complex communities

Moderator Livia Leoni

16.35-17.00	Relationships between quorum sensing signaling and biofilm development in <i>Pseudomonas aeruginosa</i>	Matthew Parsek , University of Washington, Seattle, USA
17.00-17.25	Export by a quorum sensing-controlled drug exporter underlies rifampicin's exceptional activity against strong staphylococcal biofilms	Michael Otto , NIH, Bethesda, USA
17.25-17.50	Spatially-resolved bacterial single-cell RNA sequencing links microbe-microbe communication and biofilm functional heterogeneity	Marvin Whiteley , Georgia Institute of Technology, Atlanta, USA

17.55 *Bus to the city center – free evening*

Thursday 30th October

8.30 *Bus to the meeting venue*

Session 6

Intraspecies and interspecies signaling and host-microbe interactions

Moderator Marvin Whitely

9.00-9.25	A systems biology approach to the interaction between <i>S.cerevisiae</i> and bacteria in the insect and human gut	Duccio Cavalieri , Florence University, Italy
9.25-9.50	RetS serve as a receptor in <i>Pseudomonas aeruginosa</i> that senses human-derived molecules	Liang Yang , Southern University of Science and Technology, Guangdong, China

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9.50-10.15	Actions of <i>Pseudomonas aeruginosa</i> MvfR/pqsABCDE Quorum Sensing System During Host-Pathogen Interaction	Laurence Rahme , Massachusetts General Hospital/Harvard, Boston, USA
10.15-10.30	Crosstalk in the skin: unraveling the role of <i>Staphylococcus aureus</i> in T-cell communication and disease progression in mycosis fungoides	Nazzareno Dominelli , Johannes-Gutenberg-University Mainz, Germany
10.30-10.45	The Chemical Language of the Gut-Brain Axis: Pyrazinone Signaling in Microbiota-Host Interactions	Zoe Levi , Ben-Gurion University of the Negev, Israel
10.45 11.15	<i>Coffee break</i>	

Session 7

Blocking of intercellular signaling as anti-virulence

Moderator Giordano Rampioni

11.15-11.40	Cutting off communication: a chemical approach to blocking bacterial pathogenesis	Julia Van Kessel , Indiana University Bloomington, USA
11.40-12.05	Synthetic chemical strategies to understand, alter, and divert bacterial communication pathways	Helen Blackwell , The University of Wisconsin-Madison, USA
12.05-12.20	Exploring indole signaling as a target for antivirulence therapy against enterotoxigenic <i>Escherichia coli</i> (ETEC)	Sofia Razzaq Meo , Ghent University, Belgium
12.20-12.35	The over-expression of the <i>Pseudomonas aeruginosa</i> phnAB operon abrogates its pyocyanin production possibly by interfering with PqsE expression at the post-transcriptional level	Gloria Soberon-Chavez , UNAM, Mexico
12.35-12.50	Quorum sensing coordinates a multi-layered phage defense strategy in <i>Vibrio alginolyticus</i>	Sine Lo Svenningsen , BIO, University of Copenhagen, Denmark

12.50-13.50 *Lunch break*

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Closing Keynote Lecture

Moderator Pete Greenberg

13.50–14.35	Microbial quorum sensing signals, secrets and sabotage	Miguel Cámara, University of Nottingham, UK
14.35–14.45	<i>Conclusions</i>	
14.50	<i>Bus to the city center</i>	

Please note that the conference programme is subject to change. While every effort will be made to maintain the published schedule, unforeseen circumstances may result in last-minute adjustments. Any changes will be announced during the sessions and posted on the information board. We appreciate your understanding.

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Short Programme

abstract numbers correspond to the page number in the Abstract Book

TUESDAY 28th OCTOBER

- 14.40-15.25 **Opening Keynote Lecture:** Peter Greenberg
Moderator: Miguel Cámara
Abstract 1
- 15.25-17.00 **SESSION 1:** Molecular Mechanisms of intercellular bacterial signalling
Moderator: Eric Déziel
Abstracts 2 - 6
- 17.00-17.20 Coffee Break
- 17.20-18.05 **SESSION 1 continued:**
Abstracts 7 - 9
- 18.05-19.30 **POSTER SESSION 1** – even numbers
20.00 Social Event

WEDNESDAY 29th OCTOBER

- 09.00-11.05 **SESSION 2:** Ecology and Evolution of intercellular bacterial signalling
Moderator: Ralf Heerman
Abstracts 10 - 16
- 11.05-11.30 Coffee Break
- 11.30-13.00 **SESSION 3:** Novel and emerging mechanisms of microbial communication
Moderator: Steve Diggle
Abstracts 17 - 20

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13.00-14.30 **POSTER SESSION 2** – odd numbers – with lunch

14.30-16.05 **SESSION 4:** Cooperation, Competition and Communication

Moderator: Ines Mandic Mulec

Abstracts 21 - 25

16.05-16.35 Coffee Break

16.35-17.50 **SESSION 5:** Signalling in biofilms and complex communities

Moderator: Livia Leoni

Abstracts 26 - 28

THURSDAY 30th OCTOBER

09.00-10.45 **SESSION 6:** Intraspecies and interspecies signalling and host-microbe interactions

Moderator: Marvin Whiteley

Abstracts 29 - 33

10.45-11.15 Coffee Break

11.15-12.50 **SESSION 7:** Blocking of intercellular signalling as anti-virulence

Moderator: Giordano Rampioni

Abstracts 34 - 38

12.50-13.50 Lunch Break

13.50-14.35 **Closing Keynote Lecture:** Miguel Cámara

Moderator - Peter Greenberg

Abstract 39

14.35-14.45 Conclusions

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SESSION PROGRAMME

abstract numbers correspond to the page number in the Abstract Book

1. **Acylhomoserine Lactone Quorum Sensing: What We Know and What We Want to Know.** Peter Greenberg
2. **Timing is everything: how *Pseudomonas aeruginosa* makes and breaks a quorum.** Caleb Mallery, Autumn Pope, Varun Bavda, Kayla Simanek, Amanda Kurtz, Jon Paczkowski
3. **LuxR solos mediate host specific inter-kingdom signaling in *Photorhabdus luminescens*.** Jannis Brehm, Fabio Platz, Nazzareno Dominelli, Ralf Heermann
4. **Accelerated discovery of novel quorum-sensing bypass mutations using inducible hypermutator strains of *Pseudomonas aeruginosa*.** Isabel Askenasy, Martin Welch
5. **LuxR solos as major proteobacterial players of cell-cell signaling in the plant microbiome (LuxSoM).** Cristina Bez, Alexander Martin Geller, Ofir Segev, Sonia Covacezuch, Asaf Levy, Pieter Dorrestein, Vittorio Venturi
6. **Regulatory mechanisms of mupirocin biosynthesis in *Pseudomonas fluorescens* NCIMB 10586.** Yuyuan Cai, Vittorio Venturi, Xuehong Zhang
7. **Calcium dependence and dynamics in mycobacterial cell-cell interaction,** Todd Gray, Tayler Farrington, Jill Canestrari, Ryan Clark, Keith Derbyshire
8. ***Pseudomonas aeruginosa* quorum sensing during chronic human infection.** Morgana Letizia, Marvin Whiteley
9. **RsaM – not a switch but a built-in modulator of quorum sensing in *Pseudomonas fuscovaginae*.** Nemanja Ristović, Cristina Bez, Mihael Špacapan, Michael P. Myers, Gianluca Triolo, Iris Bertani, Vittorio Venturi
10. **Interference competition mechanisms in a bacterial symbiont.** Kirsten R. Guckes, Harun Aslan, Tim I. Miyashiro
11. **Enterobacterial signalling, antibiotics and morphogen-mediated flotation.** George Salmond, Rita Monson and Ray Goldstein
12. **Quorum sensing deficiency enhances salt stress adaptation in *Bacillus subtilis* through altered gene regulation.** Tjaša Danevčič, Mihael Špacapan, Ines Mandić-Mulec

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13. **A sea of signals: quorum sensing regulates chitin degradation in marine bacterial communities.** *Mel Nie, Rachel E. Szabo, Otto X. Cordero, Rachel Gregor*
14. **Lineage and microenvironment effects drive heterogeneous quorum sensing activation in *Pseudomonas aeruginosa* microcolonies.** *Xiaohe Liu, Rolf Kümmerli*
15. **Quorum sensing plasticity in *Pseudomonas aeruginosa*: Ecological insights into strains deficient in production of 4-hydroxy-2-alkylquinolines (HAQs).** *Mylène C. Trottier, Marie-Christine Groleau, Jess Philippon, Antony T. Vincent, Eric Déziel*
16. **Dissecting cyclic lipopeptide Biosynthesis Regulation in Poly-Producing *Pseudomonas* with and without Quorum Sensing System.** *Lu Zhou, Ni Feng, Jasmine de Rop, Bishnu Prasad Marahatta, José C. Martins, Monica Höfte*
17. **Cell-cell signaling in *Haloferax volcanii*: how archaea communicate.** *Priyanka Chatterjee, Jacob Cote, Katherine Taylor, Monica McCallum, Stefan Schulze, Mecky Pohlschroder*
18. **Femtomolar signals and microalgal mating: the chemical ecology of diatom reproduction.** *Franziska Klapper, Wim Vyverman, Georg Pohnert*
19. **Unraveling Mechanisms Behind Coexistence within Microbial Ecosystems,** *Michae M. Meijler*
20. **Bacterial nanotubes emerge from a membranous organelle to establish an intercellular bridge.** *Manas Kumar Guria, Tengfei Zhong, Amit K. Baidya, Ritesh Ranjan Pal, Venkadesaperumal Gopu, Saurabh Bhattacharya, Oren Yakovian, Grant J. Jensen, Mohammed Kaplan, Ilan Rosenshine, Sigal Ben-Yehuda*
21. **Cell surface Hydrophobicity and spatial proximity impact the fitness of quorum sensing cheaters in *Pseudomonas aeruginosa*.** *Kathleen O'Connor, Nicholas Larson, Sheyda Azimi, Stephen P. Diggle*
22. **Predictive microbiome engineering.** *Lingchong You*
23. **The acquisition of additional control over quorum sensing regulation reduces the variability of final cell density.** *Marco Fondi, Christopher Riccardi, Francesca Di Patti, Francesca Vaccaro, Francesca Coscione, Alessio Mengoni, Elena Perrin*
24. ***P. aeruginosa* relies on sensing and communication systems to interact with competing opportunistic human pathogens,** *Clémentine Laffont, Ingrid Mignot, Tobias Wechsler, Priyanikha Jayakumar, Rolf Kümmerli*

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25. **Modulation of interbacterial interactions by *Pseudomonas aeruginosa* quorum sensing.** *Andrew Frando, Robert S. Parsek, Ajai A. Dandekar*
26. **Relationships between quorum sensing signaling and biofilm development in *Pseudomonas aeruginosa*.** *Matthew R. Parsek*
27. **Export by a quorum sensing-controlled drug exporter underlies rifampicin's exceptional activity against strong staphylococcal biofilms.** *Yao Liu, Lei He, Ryan Liu, Dylan J. Burgin, Min Li, Michael Otto*
28. **Spatially-resolved bacterial single-cell RNA sequencing links microbe-microbe communication and biofilm functional heterogeneity.** *Alyssa R Hamm, Gina R Lewin, Marvin Whiteley*
29. **A systems biology approach to the interaction between *S.cerevisiae* and bacteria in the insect and human gut.** *Duccio Cavalieri*
30. **RetS serve as a receptor in *Pseudomonas aeruginosa* that senses human-derived molecules.** *Yachun Zhou, Anmin Ren, Chenchen Wang, Jie Deng, Weidong Zheng, Haihua Liang, Liang Yang*
31. **Actions of *Pseudomonas aeruginosa* MvfR/pqsABCDE Quorum Sensing System During Host-Pathogen Interaction.** *Arijit Chakraborty, Shifu Aggarwal, Filip Kovacic, Arunava Bandyopadhyay, Lai Ping Wong, Vijay Singh, Rashmi Richa, Myung Whan Oh, Ruslan Sadryev, Laurence G. Rahme*
32. **Crosstalk in the skin: unraveling the role of *Staphylococcus aureus* in T-cell communication and disease progression in mycosis fungoides.** *Fred-eric Straub, Laura Serbin, Philipp Licht, Anja Schöffler, Ralf Heermann, Volker Mailänder, Nazzareno Dominelli*
33. **The Chemical Language of the Gut-Brain Axis: Pyrazinone Signaling in Microbiota-Host Interactions.** *Zoe Levi, Najah Alkrenawi, Michael M. Meijler*
34. **Cutting off communication: a chemical approach to blocking bacterial pathogenesis.** *Tanmaya A. Rasal, Caleb P. Mallery, Biqing Liang, Matthew W. Brockley, Chelsea A. Simpson, Abigail D. Padgett, Finley J. Andrew, Laura C. Brown, Jon E. Paczkowski, Julia C. van Kessel*
35. **Synthetic chemical strategies to understand, alter, and divert bacterial communication pathways.** *Helen E. Blackwell*
36. **Exploring indole signaling as a target for antivirulence therapy against enterotoxigenic *Escherichia coli* (ETEC).** *Sofia Razzaq Meo, Tom Van de Wiele, Tom Defoirdt*

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37. The over-expression of the *Pseudomonas aeruginosa* *phnAB* operon abrogates its pyocyanin production possibly by interfering with PqsE expression at the post-transcriptional level. *Alejandra Valdez, Sara E. Quiroz-Morales, Abigail González-Valdez, Valeria Cardoso-García, Selene García-Reyes, Gloria Soberón Chávez*
38. Quorum sensing coordinates a multi-layered phage defense strategy in *Vibrio alginolyticus*. *Demeng Tan, Sine Lo Svenningsen*
39. Microbial quorum sensing signals, secrets and sabotage. *Miguel Cámara*

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POSTER PRESENTATIONS

abstracts number 40 onwards

40. **Revealing New Links Between the Antibiotic Resistance Gene *aph* and Virulence in *Pseudomonas aeruginosa*.** Cemile Selin Aksoy, Paul Williams, Stephan Heeb
41. **Secondary metabolites, Fe and sugars: the multifactorial antagonism between *Bacillus subtilis* and *Pseudomonas protegens*.** Lebel-Beaucage Sandrine, Charron-Lamoureux Vincent, Bellenger Jean-Philippe, Beauregard Pascale B
42. **Light-driven selection and metabolic potential of a purple phototropic bacterial consortium cultivated on dairy waste: implications for microbial communication and biostimulant activity.** Gabriele Bellotti, Ali Amini, Andrea Turolla, Edoardo Puglisi
43. **Investigation of microbiota-mucus-host interactions within an engineered colonic simulator.** Serena Berberolli, Emily Dewhurst, Celia Ferreira, Daniel Read, Dr. Jin Seo, Francisco M. Goycoolea, Anthony Buckley
44. **Targeting the *Pseudomonas aeruginosa* las quorum-sensing system with a pyridine-based thiazolyl-hydrazone to prevent biofilm-associated infections.** Miguel M. Leitão, Nenad R. Filipovic, Manuel Simões, and Anabela Borges
45. **In situ activation of a synthetic quorum sensing circuit in *Escherichia coli* colonizing the gut of *Caenorhabditis elegans*.** Gustavo Bruschi, Marcelo Müller-Santos, Dayane Alberton
46. **Interspecies induction of biofilm development in *Bacillus subtilis*.** Jing Chen, Kisako Posthuma, Nataliia V Machushynets, Borg N.C. Bleichrodt, Caja Dinesen, Gilles van Wezel, Ákos T. Kovács
47. **Different combinations of strains from a phytopathogenic microbial consortium result in the induction or repression of pathogenic activity.** Isabel Castillo, Yax'kin Coronado, Eneas Aguirre, Mayra de la Torre
48. **Bacterial interactions in traditional milpa agroecosystems at a community level.** Eneas Aguirre-von-Wobeser, Mateo Córdoba-Agudelo, Karla Veloz-Badillo, Hernández Heriberta Hernández-Camargo, Mayra de la Torre
49. **Unraveling the potential of Quorum Sensing inter-species dialogue to restore microbiota's community dynamics.** Raphaël Defaix, Maria Ramirez-Montoya, Miguel V. Rodrigues², M. Rita Ventura, Karina B. Xavier

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50. **Cell-Cell Communication in *Pseudomonas corrugata*: A LuxR-Mediated Hierarchical System Regulates the Production of Bioactive Cyclic Lipopeptides.** Giulio Dimaria, Lu Zhou, Luca Calogero Miceli, Iris Bertani, Vittorio Venturi, Monica Höfte, Vittoria Catara
51. **Quorum sensing-mediated rhamnolipid production prevents biofilm formation of *Pseudomonas aeruginosa* on anti-attachment micro-topographies.** Manuel Romero, Jean-Frédéric Dubern, Jeni Lockett, Graziela Figueredo, Elizabeth Ison, David Scurr, Aurélie Carlier, Andrew Hook, Amir Ghaemmaghani, Jan deBoer, Morgan Alexander, Paul Williams
52. **The Effects of Natural and Environmental Metabolites on Quorum Sensing in *Pseudomonas aeruginosa*.** Osnat Gagulasvili Ifrah, Michael M. Meijler
53. **Temperature-sensitive control of RhIR links environmental cues to quorum sensing in *Pseudomonas aeruginosa*.** Sandrine Gervais, Thays de Oliveira Pereira, Marie-Christine Groleau, Nicolas Doucet, Eric Déziel
54. **PqsE is a conserved and functionally critical component of the *Pseudomonas aeruginosa* quorum sensing network.** Mylene Trottier, Marie-Christine Groleau, Jeff Gauthier, Anthony T. Vincent, Roger C. Levesque, Eric Déziel
55. **Chatting at the Extremes: How Quorum Sensing Changes Across Extreme Environments.** F. Iacuzzo, F. Migliaccio, E. Taccaliti, C. Vetriani, A. Cordone and D. Giovannelli
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Acylhomoserine Lactone Quorum Sensing: What We Know and What We Want to Know

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We witnessed the discovery of acylhomoserine lactone quorum sensing in the marine bacterium *Vibrio fischeri* in the early 1980s. In the early 1990s it became clear that this mechanism for cell-density-dependent control of gene expression was conserved among a variety of Gram-negative bacteria and that it controlled expression of virulence genes in important human and plant pathogens. It was then that the quorum sensing and response terminology and concept was introduced. We now understand details of how acylhomoserines are synthesized, how they function as a proxy for cell density and how their receptors, which are transcription factors affect gene expression. We have learned how quorum sensing can be employed to facilitate cooperative behavior, and quorum-sensing control of cooperation has become a model for studies of the evolution of cooperation. Most of our knowledge about quorum sensing comes from studies of pure cultures in the laboratory. In fact, *V. fischeri* quorum sensing is critical for the monospecific lifestyle of this species in light organs of certain marine animals. For pathogens like *Pseudomonas aeruginosa* quorum sensing is thought to be important in infections where other bacterial species also exist. We also know that quorum sensing signals exist in more complex polymicrobial environments like plant root environments and even human intestinal environments. How and why signaling occurs and signals are deciphered in these environments remain important questions. We now know from queries of metagenomic databases there are thousands of unique acylhomoserine lactone quorum sensing gene cassettes, however we know the chemistry of the quorum sensing signals of precious few bacteria. I will discuss progress in solving the problem of predicting signals from gene sequences and how this can advance understanding of quorum sensing in polymicrobial environments.

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Timing is everything: how *Pseudomonas aeruginosa* makes and breaks a quorum.

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A bacterial infection is not a static event. Bacteria must first colonize a host, proliferate, survive, and then disseminate into a new host. Microbial adaptation, both at the genetic and signaling systems levels, is key to an infection to ensure the success of the bacteria. *Pseudomonas aeruginosa* is an opportunistic pathogen that causes tens of thousands of hospital-acquired infections each year. *P. aeruginosa* is highly mutable, allowing it to grow in different environments, including on abiotic surfaces. The mutability also allows it to develop resistance to antibiotics, often creating a reservoir of highly drug-resistant subpopulations in the environment or in the host. *P. aeruginosa* persists in healthcare settings by colonizing ventilators and catheters and forming biofilms on medical equipment. Biofilm formation and pathogenesis in *P. aeruginosa* are regulated by quorum sensing (QS). QS is a mechanism of bacterial communication that controls the expression of genes involved in virulence and pathogenesis in many bacteria via the population-wide synchronous response of transcriptional regulators to secreted signaling molecules called autoinducers (AI). *P. aeruginosa* QS is coordinated through a complex signaling network that involves two homologous homoserine lactone (HSL) AI/receptor pairs: 3OC12HSL/LasR and C4HSL/RhIR. Canonically, sitting atop the hierarchy, LasR activated by 3OC12HSL upregulates the *rhl* system. RhII synthesizes C4HSL, which binds RhIR to activate it as a transcriptional regulator. RhIR is further regulated via a direct interaction with the metallo-hydrolase, PqsE. The RhIR-PqsE complex exhibits a higher affinity for promoter DNA than RhIR alone, thereby enhancing RhIR-dependent signaling. LasR promotes and RhIR represses the expression of *pqsE*, respectively, highlighting the complex interwoven network of QS signaling. Additionally, many clinical isolates evolve *lasR* inactivating mutations while accruing concurrent single-nucleotide polymorphisms (SNPs) in other QS genes, while largely maintaining RhIR signaling. This nuance highlights the plasticity of QS in *P. aeruginosa* during an infection. The overarching goal of my research program is to understand the basic mechanistic principles that drive gene regulation, particularly through RhIR-dependent transcription, and how these processes allow for adaptive signaling progression to initiate and maintain an infection using the *P. aeruginosa* QS pathway as a model.

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LuxR solos mediate host specific inter-kingdom signaling in *Photorhabdus luminescens*

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Bacteria and their hosts communicate through a variety of hormone-like signals in a process known as inter-kingdom signaling. This communication involves bacterial molecules influencing eukaryotic cell signaling, while host hormones can interact with bacterial cell-to-cell communication systems. In Gram-negative bacteria, such communication is typically mediated by LuxR-type receptors, which are often part of quorum sensing systems. However, many bacteria also contain so-called LuxR solos, orphan LuxR-type receptors that lack a paired signal synthase, which can play roles in both bacterial and inter-kingdom communication. The Gram-negative insect pathogen *Photorhabdus luminescens* possesses an unusually high number of 40 LuxR-type receptors, making it a highly versatile communicator. Throughout its complex life cycle, *P. luminescens* alternates between two phenotypic states: primary (1°) cells and secondary (2°) cells, which differ in diverse phenotypic traits. The latter are strongly attracted to plant root exudates, facilitating root colonization and providing plants with protection against phytopathogenic fungi. While both cell types are highly pathogenic to insects, only 1° cells can establish symbiosis with nematodes, which serve as vectors for transferring the bacteria from one insect host to another.

In this study, we identified two LuxR solos primarily involved in inter-kingdom signaling between *P. luminescens* and its eukaryotic hosts. The first is the LuxR solo pair PikR1/PikR2, which detects insect-derived signals and regulates insect pathogenicity of 1° cells. To determine the chemical nature of the signals sensed by PikR1/PikR2, homogenates from *Galleria mellonella* larvae were fractionated via HPLC, and the active fractions were analyzed using LC-MS. This led to the identification of stearic acid and palmitic acid, two of the most abundant fatty acids in the *G. mellonella* fat body, as the key signaling molecules. The second LuxR solo, SdiA, is involved in plant root colonization capabilities of the 2° cells and responds to plant-derived signals. Using surface plasmon resonance spectroscopy and nano differential scanning fluorimetry on purified SdiA, we obtained initial evidence that SdiA responds not only to acyl-homoserine lactones (AHLs), but also to indole compounds and ethanolamines, molecules commonly found in plant root exudates.

In summary, our findings reveal that LuxR solos in *P. luminescens* play a crucial role in inter-kingdom signaling, enabling the bacteria to modulate its pathogenic and mutualistic interactions with their diverse eukaryotic hosts.

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Accelerated discovery of novel quorum-sensing bypass mutations using inducible hypermutator strains of *Pseudomonas aeruginosa*

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Quorum sensing (QS) is a hierarchical intercellular communication system that enables bacteria to detect their population size and respond accordingly to optimize the utilization of available resources. In *Pseudomonas aeruginosa*, QS controls the expression of a wide set of genes, many of which are considered virulence factors. *P. aeruginosa* QS relies on the secretion of autoinducer molecules, OdDHL and BHL, which are sensed by their corresponding cognate transcription factors, LasR and RhIR (respectively). However, in clinical isolates, loss-of-function *lasR* mutants are common, yet in many cases these retain virulence, indicating that QS "bypass" mechanisms exist. To further investigate the genetic basis for such bypass mechanisms, we utilized an inducible hypermutator (HM) strain in which the rate of mutation can be "tuned" by the experimenter. We then introduced *lasR* or *rhIR* knockout mutations into the HM background, and screened for mutants in which virulence and/or QS-regulated gene expression was restored. Our data revealed that secreted protease production can be restored in the *DlasR* background by mutations in the transcription factor *mexT*. However, other *DlasR* bypass mutations were also identified. In parallel, we also looked for secondary mutations that bypass RhIR-dependent gene expression. This posed a more significant challenge because the *DrhIR* strain lacked a readily screenable phenotype, such as protease secretion. Instead, we introduced *lacZ* fusions downstream of RhIR-dependent promoters, enabling facile visual and quantitative assessment of bypass mutants. Using both screens, we have identified a number of target genes for further characterization in both genetic backgrounds.

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LuxR solos as major proteobacterial players of cell-cell signaling in the plant microbiome (LuxSoM)

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Quorum sensing (QS) mediated by LuxI/LuxR modules and N-acyl-homoserine lactones (AHLs) is a well-established mechanism of bacterial communication. However, our current understanding is largely shaped by in vitro studies of model pathogens and symbionts, which do not fully capture the complexity of natural microbial ecosystems. Recent findings indicate that LuxI/LuxR systems are uncommon in natural habitats such as the plant microbiome. Instead, LuxR solos - QS-related transcriptional regulators that lack co-localized LuxI synthases — are widespread and frequently found adjacent to biosynthetic gene clusters (BGCs), suggesting a divergence from AHL detection toward novel endogenously produced metabolites. This so-called "dark metabolome" includes structurally diverse and ecologically adapted compounds, reflecting communication strategies optimized for natural, heterogeneous habitats. However, our understanding of these alternative signaling systems and their roles in interspecies interactions remains very limited.

Through the LuxSoM project funded by the MSCA Global Action, we applied a reverse-genomics strategy using LuxR solos as bait to identify BGCs overlooked by available genome mining pipelines. These LuxR-BGC loci were dereplicated based on domain content, order, and sequence identity. Selected pairs were subjected to targeted gene knock-outs followed by untargeted LC-MS/MS metabolomics, revealing unique unannotated chemical features. Molecular networking linked them to known and biologically relevant compound families. Future work will focus on validating their signaling function using biosensor-based assays and assessing their ecological roles in synthetic microbial communities (SynComs). This study reveals a potentially widespread, previously overlooked mode of bacterial communication and lays the foundation for microbiome-level manipulation through native microbiome-derived signal molecules.

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Regulatory mechanisms of mupirocin biosynthesis in *Pseudomonas fluorescens* NCIMB 10586

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Mupirocin is a clinically important antibiotic produced by *Pseudomonas fluorescens*. Mupirocin biosynthesis is regulated by quorum sensing (QS) via the N-acyl-homoserine lactone (AHL) dependent *mupI/R* system. However, studies on its regulatory mechanisms remain scarce, and the construction of engineered strain with high-yield mupirocin has not been reported. Here, we found that the atypical QS gene arrangement, *mupR-mupX-mupI-rsaL*, is closely related to the mupirocin biosynthetic gene cluster. *MupR* was found to activate the transcription of multiple locus within *mup* BGC, whereas *RsaL* was shown to repress *mupI* expression by binding to the promoter region. The inactivation of *MupX* influenced the proportion of mupirocin compounds. Co-expression of *mupR* with *mupO*, *mupF*, or *macpC* increased the production of pseudomonic acid A (PA-A), the most bioactive component. A plasmid-free strain of high-titer PA-A production was engineered by integrating multi-copy *mupR* into the genome. In summary, we further elucidated the regulatory role of the *mupR-mupX-mupI-rsaL* locus in mupirocin biosynthesis and successfully engineered strains with enhanced mupirocin production.

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Calcium dependence and dynamics in mycobacterial cell-cell interaction

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Extant bacteria are the successful products of over a billion years of selection in crowded and competitive niches. Mechanisms for detecting and responding to non-kin cells have likely evolved to be fixtures in bacterial genomes but their function(s) in interaction biology may go undetected in traditional reductive monoculture studies. Mycobacteria are a diverse genus that include historic as well as emerging pathogens, but mycobacterial interaction mechanisms are not well described. We have begun addressing that gap by exploiting conjugation between different strains of *Mycobacterium smegmatis*. This experimental system has revealed a novel kin-recognition system, roles for two specialized ESX secretion systems and is continuing to define a cell-contact-initiated signal transduction network that is assigning biological functions to genes that had eluded previous description. Contact with a conjugative donor cell elicits a signal transduction pathway response in the recipient cell that includes the extracytoplasmic function sigma factor M (SigM). SigM's 12 transcript regulon includes genes that encode a specialized secretion system, ESX-4, and other genes of undefined function. Here we demonstrate that a singleton SigM regulon gene encodes a protein with repeated calcium-binding motifs and that the recipient requires this protein for conjugation. To test whether calcium plays a role in conjugation, we used calcium chelators and found that free calcium is required for conjugation. Chelation prevented cell contact-initiated activation of SigM-ESX-4, thereby connecting calcium to both the donor contact stimulus and the induction of SigM as a recipient response to contact. We visualized a fluorescent reporter of intracellular free calcium in our conjugative cells and we observe fluorescence events in cells that contact a mating partner. Findings from these complementary approaches identify calcium as a critical element in our contact-initiated signal transduction pathway to ESX-4. Gene conservation suggests that calcium-dependent contact signaling underpins beneficial mycobacterial interactions.

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***Pseudomonas aeruginosa* quorum sensing during chronic human infection**

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Over the past three decades, extensive research has uncovered the complexity of quorum sensing (QS) in *Pseudomonas aeruginosa*, revealing how this bacterial communication system coordinates the expression of numerous virulence factors in a cell-density-dependent manner. Although considerable work has elucidated the properties of QS in vitro, the extent to which these social behaviors are active during human infection remains unclear. We used RNA-seq data to investigate the expression of QS-controlled genes in 44 *P. aeruginosa* transcriptomes from chronic human infections, including cystic fibrosis (CF) lung and soft-tissue wound infections. We performed a differential expression analysis comparing a PAO1 lasI-rhlI QS mutant strain grown to late exponential phase with and without added acyl-homoserine lactones to define QS ON/OFF states. To assess the degree to which social behaviors are active in chronic human infections, we focused on a core set of 90 genes that were QS-activated in strain PAO1 and expressed during chronic human infection. Twenty-nine of these genes were classified as QS OFF in both CF lung and wound samples, showing four- to 190-fold reductions in expression compared with the in vitro QS ON state. These included genes encoding the LasA and LasB proteases, protease IV, the alkaline protease AprA and its inhibitor AprI, the ChiC chitinase, the ClpP2 peptidase, and the PqsH monooxygenase necessary for PQS signal synthesis. Eleven genes showed expression levels similar to the QS ON state in both CF lung and wound samples, including those encoding the transcriptional regulator RsaL and the PqsABCDE enzymes involved in HHQ signal synthesis. Eight genes were categorized as QS ON in one chronic human infection type but not the other. The remaining 42 genes showed variable expression in humans. Overall, this study provides a detailed view of the QS-controlled regulon in *P. aeruginosa* during chronic human infection.

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RsaM – not a switch but a built-in modulator of quorum sensing in *Pseudomonas fuscovaginae*

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Pseudomonas fuscovaginae, a major rice pathogen, possesses two archetypical quorum sensing systems called PfsI/R and PfvI/R, both of which are inactive under in vitro conditions, but active in planta. Previously, a random Tn5 mutant with transposon insertion between the pfsI and pfsR genes was found to have a hyperactive PfsI/R system. More precisely, the Tn5 inserted in the gene promoter region of an ORF encoding for RsaM, a putative protein that has been hypothesized to play a central role in imposing repression on the PfsI/R system. In this model, RsaM represented a switch element likely to respond to an unknown stimulus/signal that unlocks the PfsI/R system. In the present study, we aimed to confirm that RsaM is indeed expressed and determine its place within the PfsI/R regulatory circuit. We used targeted mutagenesis, along with promoter, transcriptome, and protein studies to show that RsaM is not produced in the wild-type *P. fuscovaginae* and does not contribute to keeping the PfsI/R system shut down. On the other hand, the expression of RsaM is triggered upon targeted introduction of a large insertion in the pfsR/rsaM intergenic region, and accompanies increased levels of both the pfsI and pfsR transcription. Moreover, we demonstrate that RsaM acts as a repressor of the PfsI/R circuit in this genetic background, although its molecular mechanism of action remains unknown. Taken together, our results evidence that RsaM acts as a built-in modulator that prevents overactivation of an already derepressed PfsI/R system, rather than a switch.

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Interference competition mechanisms in a bacterial symbiont

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Vibrio fischeri is a bioluminescent bacterium that establishes symbiosis with the Hawaiian bobtail squid *Euprymna scolopes*. Within a symbiotic light organ, quorum sensing by populations of *V. fischeri* results in bioluminescence production, which the squid host uses for a camouflaging behavior called counterillumination. Recent work found that quorum sensing also inhibits the expression of a type-6-secretion system (T6SS), which enables certain strains to kill susceptible neighboring bacterial cells through the delivery of toxic effectors. Here, I describe the development of a model to study intercellular interactions between two T6SS+ strains of *V. fischeri*. Each strain exhibits the ability to inhibit the growth of the other strain in a manner that depends on T6SS. While the structural components of the T6SS are highly conserved among strains, putative effectors display remarkably diverse primary sequences. Ectopic expression of an AHH nuclease effector and its immunity factor from one strain is sufficient to promote kin growth inhibition in the other strain, unless the other strain harbors the immunity factor. Finally, a mechanism describing how the foreign effector is loaded onto the T6SS is presented. Taken together, these findings represent the first experimental evidence of a toxic effector in *V. fischeri*, which provides insight into the molecular mechanisms governing interference competition between bacterial symbionts.

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Enterobacterial signalling, antibiotics and morphogen-mediated flotation

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We investigated the production of quorum sensing (QS) molecules (N-acyl-homoserine lactones; N-AHLs) in the regulation of plant pathogenesis and antibiotic production in Gram-negative enterobacteria (*Erwinia*: *Pectobacterium* - and *Serratia*: *Prodigiosinella confusaribida*/*Prodigiosinella aquatilis* ATCC 39006). The biogenesis and active secretion of plant cell wall-degrading enzymes is bacterial cell density-dependent and controlled by prior elaboration of freely diffusible N-AHLs. Production of two antibiotics (the beta-lactam: 1-carbapen-2-em-3-carboxylic acid) and a red-pigmented prodiginine: prodigiosin) is modulated by QS. Analysis of white mutant derivatives defective in prodigiosin biogenesis, coupled with light microscopy and electron microscopy, revealed that intracellular gas vesicles (GVs) were produced in a QS-dependent fashion. Production of intracellular GV was also affected by oxygen availability modulating capacity for bacterial flotation. In summary, the *Serratia* strain made two biochemically unrelated antibiotics and GV, all under QS control.

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Quorum sensing deficiency enhances salt stress adaptation in *Bacillus subtilis* through altered gene regulation

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Bacterial cell–cell communication via quorum sensing (QS) plays a central role in coordinating collective behaviors in response to environmental changes. In *Bacillus subtilis*, the ComQXPA QS system modulates important physiological processes such as competence development, surfactin production, biofilm formation, and the expression of extracellular enzymes. In our study, we explored how disruption of this QS system influences the ability of *B. subtilis* to adapt to high-salinity stress. We compared the PS-216 wt strain to a QS-deficient ΔcomQ mutant, which lacks the ComX signaling peptide and is therefore unable to activate the ComQXPA pathway. Phenotypic analyses revealed that while the wt strain displayed salinity-dependent changes in colony morphology, the ΔcomQ mutant maintained consistent colony size across all tested NaCl concentrations on solid SMM and MSgg media. To uncover the regulatory effects underlying this phenotype, we monitored the promoter activity of proline biosynthesis and biofilm-related genes (i.e. *proHJ*, *epsA*) in liquid MSgg medium at different salinity levels during static growth. The ΔcomQ mutant exhibited earlier and stronger activation of the *proHJ* promoter at elevated salt concentrations, indicating a faster and more robust osmotic stress response compared to the wt strain. Moreover, higher expression of the *epsA* promoter in the ΔcomQ mutant suggested enhanced potential for biofilm production under stress conditions. These results demonstrate that the loss of QS signaling through the ComQXPA system modifies the transcriptional response to osmotic stress, enhancing adaptability and altering multicellular behavior. Our findings highlight the dynamic relationship between cell–cell communication and environmental sensing in bacteria, offering new perspectives on how QS networks integrate stress signals to regulate adaptations.

"Cell-cell communication in bacteria: new insights and future trends"

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A sea of signals: quorum sensing regulates chitin degradation in marine bacterial communities

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Small molecules are the currency of the microbial world, as their production, consumption, and exchange underpin the most basic processes of microbial existence. The importance of trophic interactions (e.g. cross-feeding of simple sugars and acids) in microbial communities is well-established. However, interactions based on specialized metabolites remain an often-hidden variable in community assembly and function.

For example, quorum sensing (QS), a form of bacterial communication based on small molecule signals, has been extensively studied in marine model organisms. However, QS has proven challenging to characterize in natural communities, likely because it encompasses a wide diversity of signals, bacteria, and phenotypes.

Here, I describe a bottom-up approach to study QS in marine bacterial communities that degrade particulate organic matter, a key crossroads in the marine carbon cycle. To do so, we characterize a collection of 150 particle-associated bacterial isolates from coastal seawater, through genomics, metabolomics, and functional assays. I will discuss the prevalence and impact of QS in these communities, and implications for the rate of particulate organic matter degradation in the oceans.

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Lineage and microenvironment effects drive heterogeneous quorum sensing activation in *Pseudomonas aeruginosa* microcolonies

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Quorum sensing (QS) is a bacterial cell-cell communication process involving the production, detection, and response to extracellular signaling molecules known as autoinducers. QS enables bacteria to sense population density and coordinate collective behaviours such as swarming and biofilm formation. While traditionally thought to be activated uniformly within a population, recent studies revealed substantial heterogeneity in QS gene expression even among clonal cells. We hypothesize that this heterogeneity is driven by stochastic effects at the onset of QS, which are then amplified in spatially structured environments due to the limited diffusion of autoinducers and local cell-to-cell interactions. To investigate QS heterogeneity, we grew *Pseudomonas aeruginosa* PAO1 strains with single-copy gene expression reporters on agarose pads and used time-lapse fluorescence microscopy to monitor microcolony formation and QS activation at single cell resolution. Using deep learning-based cell segmentation and tracking tools, we explored temporal, spatial, and lineage effects for QS activation and propagation for the two homoserine lactone-based QS systems (Las and Rhl).

We observed high heterogeneity in the expression of autoinducer synthesis genes (*lasI* and *rhlI*), whereas the cognate receptor genes (*lasR* and *rhlR*) and effector genes (*lasB* and *rhlAB*) were more homogeneously expressed across cells. This pattern suggests an initially stochastic activation of autoinducer production that later propagates to nearby cells, resulting in hotspots of QS activation within colonies. Training a random forest regressor on our single-cell dataset results in models achieving high accuracy in predicting *lasI* and *rhlI* expression. These models reveal that heterogeneity in QS signal gene expression levels was predominantly explained by cell lineage effects (~95%), meaning that sister cells have significantly more similar expression profiles than neighbouring or random cells. Conversely, spatial proximity (neighbourhood) explained only 3% of gene expression variation. These results indicate that QS-signal production is primarily driven by a few high expressing cell lineages, whereas induction of signal production in neighbouring cells via signal diffusion seems rare. These findings provide key insights in the role of cell lineages and local microenvironments in shaping QS activation in *P. aeruginosa* and the regulation of bacterial social behavior in spatially structured communities.

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Quorum sensing plasticity in *Pseudomonas aeruginosa*: Ecological insights into strains deficient in production of 4-hydroxy-2-alkylquinolines (HAQs)

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Pseudomonas aeruginosa is an opportunistic pathogen involved in various infections. Its innate resistance to many antibiotics limits treatment options, emphasizing the need for alternative strategies. Among these, quorum sensing (QS) remains a promising anti-virulence target. This bacterium possesses three interconnected QS systems: las, rhl, and pqs. The pqs system is driven by signaling molecules called 4-hydroxy-2-alkylquinolines (HAQs) (also known as 2-alkyl-4-quinolones), with MvfR (PqsR) as its LysR-type transcriptional regulator. Upon binding HAQs such as 4-hydroxy-2-heptylquinoline (HHQ) or 3,4-dihydroxy-2-heptylquinoline (PQS), MvfR activates the transcription of the pqsABCDE operon, which encodes HAQ biosynthesis enzymes. The final gene in this operon, pqsE, encodes a multifunctional protein involved in both HAQ production and the regulation of virulence determinants such as pyocyanin, through its interaction with the LuxR-type transcriptional regulator RhlR. Approximately 20% of *P. aeruginosa* isolates, whether from clinical and environmental sources, lack HAQ production – a phenotype also seen in the closely related species *Pseudomonas paraaeruginosa*, where it constitutes a notable feature of its QS system. We confirm this phenotype in four *P. aeruginosa* strains and investigate the associated genomic and functional variations. Naturally evolved HAQ-negative strains harbor diverse mutations in the pqs operon or mvfR, suggesting convergent evolution leading to HAQ deficiency. Despite lacking HAQs, these strains retain traits associated with HAQ signaling and PqsE activity, including biofilm formation and the production of pyocyanin, which suggests the presence of compensatory or alternative regulatory mechanisms. To assess broader QS adjustments, we further measured the production of acyl-homoserine lactone molecules (3-oxo-dodecanoyl-homoserine lactone (3-oxo-C12-HSL) and butanoyl-homoserine lactone (C4-HSL)), the signaling autoinducers of the las and rhl QS systems, respectively.

Our findings highlight the regulatory flexibility of *P. aeruginosa* and the potential for QS rewiring in HAQ-negative strains. These isolates provide insight into alternative virulence pathways and offer a foundation for designing more effective QS-targeted therapeutic strategies.

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Dissecting cyclic lipopeptide Biosynthesis Regulation in Poly-Producing *Pseudomonas* with and without Quorum Sensing System

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The plant microbiome represents a vast, underutilized reservoir of genes and bioactive compounds with potential applications in agriculture and medicine. *Pseudomonas mediterranea* EDOX and *Pseudomonas cichorii* SF1-54, were previously isolated respectively from the leaf endosphere of a tomato plant in the Netherlands and diseased butterhead lettuce in Belgium. Both strains show strong antagonism against the plant pathogenic fungus *Rhizoctonia solani* AG2-1 and were further characterized through complete genome sequencing and bioinformatic analyses. The full genome was assembled using PacBio sequencing combined with Illumina reads, revealing several complete non-ribosomally synthesized peptide synthetase (NRPS) gene clusters associated with lipopeptide biosynthesis. Specifically, *P. mediterranea* EDOX harbored gene clusters for the production of cormycin (CLP), medipeptin (CLP), and thanafactin (LLP), while *P. cichorii* SF1-54 encoded clusters for pseudomycin (CLP), cichozeptin (CLP) and cichofactin (LLP). Notably, the organization of lipopeptide biosynthetic gene clusters (BGCs) differed between the two strains. the pseudomycin-cichozeptin BGC in SF1-54 lacked a quorum sensing (QS) regulatory system, However, three LuxR-type regulatory genes (*cipR1*, *cipR2*, and *cipR3*) are located downstream of the cichozeptin NRPS genes and are implicated in the regulation of pseudomycin-cichozeptin biosynthesis. Among them, *cipR2* encodes an AHL-binding domain, suggesting a potential role in QS-mediated regulation. In contrast, the cormycin-medipeptin BGC in EDOX included a QS regulatory system, indicating distinct mechanisms of lipopeptide regulation. To this end, functional genomic studies were conducted by knocking out LuxR-type regulators of the cormycin-medipeptin BGC in *P. mediterranea* EDOX, and pseudomycin-cichozeptin BGC in SF1-54 revealing their critical role in the production of antimicrobial compounds. Regulation of these LPs appears to be different in these two strains: CorF and Quorum sensing (QS) regulated in EDOX while *CipR1*, *CipR2*, *CipR3*, *CifR1* and *CifR2* regulated in SF1-54. However, how these regulators function in activating LP production is unknown. In vitro antifungal activity assays confirmed that these regulators are essential for synthesizing bioactive molecules with antifungal activity against *Rhizoctonia solani* AG2-1. Further investigations are needed to elucidate interactions among LuxR-type regulators and their detailed roles in the regulation of antimicrobial production in EDOX and SF1-54. This work lays the foundation for future studies on regulatory networks and bioactive compound synthesis, with promising implications for agricultural and pharmaceutical applications.

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Cell-cell signaling in *Haloferax volcanii*: how archaea communicate

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Archaea are critical players in global biogeochemical cycles, important members of human-associated microbiomes, and contribute unique biochemical capabilities with applications in biotechnology and bioremediation. Yet fundamental aspects of their cell biology, such as cell-cell communication, remain poorly understood. While quorum sensing (QS) is widespread in bacteria, little is known about analogous processes in archaea. We have developed *Haloferax volcanii* as the first robust archaeal model for QS studies, revealing that QS controls two readily quantifiable phenotypes: swimming motility and cell shape transitions. We determined that the QS signal is a secreted, potentially novel small molecule, and activity-guided purification is underway to identify its chemical structure. Forward genetic screens identified mutants defective in producing or secreting the signal, as well as mutants unable to respond to it, uncovering the involvement of a potential two-component regulatory system. Furthermore, quantitative proteomics showed that in the presence of the conditioned medium, 236 proteins are differentially abundant in wild type, indicating that cell-cell signaling have wide-ranging effects on the proteome. Finally, we showed that supernatants from certain halophiles can trigger the *H. volcanii* QS response, whereas others cannot, and that *H. volcanii* produces a compound capable of activating a bacterial QS bioreporter. These findings indicate that archaeal QS participates in intra- and interspecies, as well as interdomain, communication. This work establishes the first experimentally tractable archaeal QS system, uncovers new components of archaeal communication pathways, and provides a foundation for exploring conserved and domain-specific principles of microbial signaling across the tree of life.

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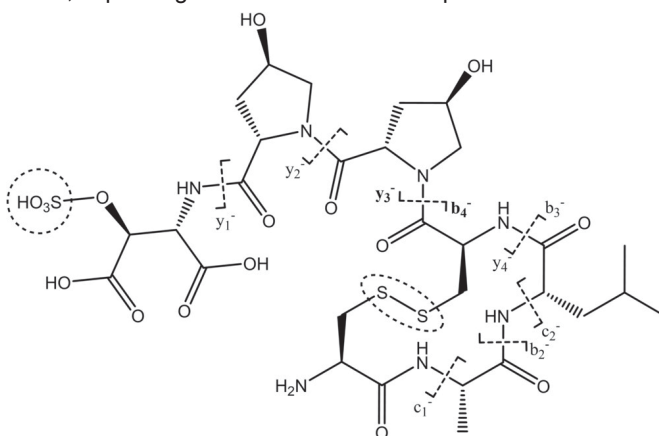
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Femtomolar Signals and Microalgal Mating: The Chemical Ecology of Diatom Reproduction

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Diatoms are abundant unicellular microalgae, responsible for ~ 20% of global photosynthetic CO₂ fixation. Despite of this importance for primary productivity and climate functioning, we know little about fundamental aspects of their biology, such as their sexual reproduction. Pheromone-mediated chemical communication is crucial for successful mating. We will introduce how an attraction pheromone was identified in the diatom *Seminavis robusta* using a comparative metabolomics approach. Additional metabolites that prime cells for sex and synchronize the search and mating behavior remained elusive. These sex-inducing pheromones (SIP) induce cell cycle arrest and trigger the production of the attraction pheromone. In this contribution we also describe the challenging structure elucidation of an *S. robusta* SIP. Essential was the use of isotope labeling paired with mass spectrometry to decipher the unprecedented hydroxyproline and β -sulfated aspartate-containing cyclic heptapeptide. Having the structure in hands we determined that the pheromone acts in only femtomolar concentrations, explaining the low amounts of the pheromone in sexually active cultures.



F. Klapper et al. Angew. Chem. Int. Ed. <https://doi.org/10.1002/anie.202307165>

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Unraveling Mechanisms Behind Coexistence within Microbial Ecosystems

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Life on earth is heavily based on chemical communication between cells. Quorum sensing enables unicellular organisms to coordinate their behavior and function in such a way that they can adapt to changing environments and compete, as well as coexist, with multicellular organisms. Prime examples of this phenomenon are displayed by the opportunistic pathogens *Pseudomonas aeruginosa* and *Staphylococcus aureus*, which cause disease in humans – but most often do not. In recent years we embarked on a quest to unravel questions regarding coexistence, based on chemical signaling. The Meijler group is targeting and examining signaling within and between various microbes (e.g. pathogens in humans and beneficial soil microbes) with several chemical tools, such as a set of electrophilic and photoactivatable 'tag-free' probes that are designed to bind QS receptors covalently. These probes are used as molecular tools to obtain new insights into the mechanisms of activation, deactivation and recognition of bacterial quorum sensing. Diverse species, including eukaryotes, have been found to react strongly to the presence of these compounds, and the recognition of QSMs is mediated by mostly unknown receptors. Recently we identified and validated the role of a human receptor for HSLs, called the Major Vault Protein (MVP), as an important immunomodulator, and we also identified new receptors for QSMs in other species. We also recently identified an exciting new mode of coexistence between bacterial pathogens using untargeted metabolomics and synthetic confirmation, and we are developing new ABPP probes to identify the unknown receptors that mediate these events.

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Bacterial nanotubes emerge from a membranous organelle to establish an intercellular bridge

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Microbial communication via contact-dependent interactions are ubiquitous in nature. Bacterial cells engage intercellular communication to coordinate their activities within their social environment. Bacteria can employ membranous conduits, termed nanotubes, that facilitate cell-to-cell communication through direct intercellular contact. Initially discovered in our laboratory, bacterial nanotubes have been found to act as channels for the exchange of metabolites, cytoplasmic proteins, and even non-conjugative plasmids between neighbouring cells. However, the real-time visualization of membranous nanotubes, including their formation, kinetics, and the establishment of an intercellular bridge has been challenging. Here, we developed a live-cell imaging microscopy-based methodology to capture the real-time protrusion of bacterial nanotubes and their dynamics in living *Bacillus subtilis* cells. Our findings reveal that nanotubes rapidly emerge from lipid-rich membrane sites within milliseconds and elongate into a few micron length. Cryo-ET analysis of these lipid-rich membrane sites revealed stacks of membrane invaginations emerging from the cytoplasmic membrane, folded into multilayered, rolled membrane tubes that resemble mesosome-like structures. Subsequent their emergence, nanotubes exhibit dynamic, multidirectional movement toward neighbouring cells, actively scanning the surfaces. During this dynamic searching process, lytic enzymes are deposited by nanotubes to locally disrupt the recipient's cell wall, enabling the nanotube to penetrate and establish an intercellular membranous bridge. This study represents the real-time visualization of bacterial nanotube-mediated intercellular bridging, the first-ever observation of any intercellular bridge formation, offering new insights into the contact-dependent interaction and cell-cell communication in bacteria.

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Cell surface Hydrophobicity and spatial proximity impact the fitness of quorum sensing cheaters in *Pseudomonas aeruginosa*

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Bacterial pathogens utilize social behaviors to cooperate and modify their environment, facilitating colonization and survival. In *Pseudomonas aeruginosa*, cooperation is mediated by quorum sensing (QS), which regulates the production of public goods, such as exoproteases. However, QS-deficient mutants (cheaters) exploit these public goods without contributing, raising questions about how cooperation is maintained. Here, we investigate how spatial structuring and cell surface hydrophobicity influence bacterial aggregation and the fitness of cheaters in a polymer-structured liquid medium that promotes aggregate formation. Using confocal microscopy and image analysis, we previously demonstrated that aggregation patterns are primarily driven by cell surface hydrophobicity, with hydrophilic wild-type (PAO1) forming "stacked" aggregates and a hydrophobic O-specific antigen deficient cells (PAO1 Δ sag) forming "clumped" aggregates. Mixed populations of differing surface properties segregate into distinct aggregates, limiting interactions between cooperators and cheaters. Nearest-neighbor distance measurements reveal that spatial segregation influences cheater fitness, where cheaters with hydrophilic cell surface maintain higher proximity to cooperators in social environments. Additionally, we find that cheaters with hydrophobic cell surface exhibit lower fitness than hydrophilic cheaters, suggesting that surface properties influence social interactions. Our results indicate that spatial structuring at the micron scale plays a crucial role in maintaining cooperation by restricting cheater access to public goods. These findings have implications for bacterial infections, particularly in the cystic fibrosis lung, where aggregates, QS mutants and LPS variations are commonly observed. Understanding how biophysical properties shape bacterial social dynamics may inform strategies to mitigate pathogen persistence and antibiotic tolerance.



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Predictive microbiome engineering

Lingchong You

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Predictive control of microbial communities presents a daunting challenge, due to numerous interactions among community members, mobile genetic elements, and environmental influences. However, our computational and experimental analysis has uncovered an emerging simplicity beneath this complexity. In this talk, I will share how we have used machine learning to reveal hidden simplicity in microbial dynamics, uncovering low-dimensional representations that capture the essential behaviors of these systems. In parallel, we have developed coarse-grained models that attempt to describe these dynamics in a simplified yet effective manner. Moreover, I will discuss horizontal gene transfer (HGT) as nature's approach to coarse graining, enabling the stabilization and predictability of functional dynamics within microbial communities without needing to fully capture their compositional dynamics. Together, these perspectives suggest the possibility of scalable and precise microbiome engineering for applications in medicine and biotechnology.

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The acquisition of additional control over quorum sensing regulation reduces the variability of final cell density

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Bacteria usually possess more than one quorum sensing (QS) regulatory modules that sometimes form complex regulatory networks. These configurations have evolved through the integration of novel transcription factors into the native regulatory systems. However, the selective advantages provided by these alternative configurations on QS-related phenotypes is poorly predictable only based on their underlying network structure. Here, we show that the acquisition of extra regulatory modules of QS has important consequences on the overall regulation of microbial growth by significantly reducing the variability in the final cell density in *Burkholderia*. By mapping the distribution of horizontally transferred QS modules in extant bacterial genomes, we found that these tend to add up to already-present modules in the majority of cases. We then selected a strain harboring two intertwined QS modules and, using mathematical modelling, we predicted an intrinsic ability of the newly acquired module to buffer the variability in the final cell density. We validated this prediction choosing one strain possessing both systems, deleting one of the two and measuring parameters such as cell density and QS synthase promoter activity. Finally, using transcriptomics, we show that the de-regulation of metabolism likely plays a key role in differentiating the two configurations.

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P. aeruginosa relies on sensing and communication systems to interact with competing opportunistic human pathogens

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Polymicrobial infections, in which multiple pathogens coexist, are common. Yet, little is known about how these pathogens communicate and interact with each other. The concept of competition sensing claims that bacteria detect cues such as nutrient limitation or cell damage to regulate their behavior toward other cells. While intuitive as a concept, the molecular mechanisms underlying competition sensing, and whether they are general or tailored to specific competitors and environments, remain largely unknown. Here, we explored how *Pseudomonas aeruginosa* senses and reacts to six other opportunistic human pathogens that often co-occur in polymicrobial infections: *Acinetobacter baumannii*, *Burkholderia cenocepacia*, *Escherichia coli*, *Enterococcus faecium*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*. To mimic distinct conditions, we designed three interaction assays: a supernatant assay to test the effects of secreted compounds, and co-culture assays to assess direct, cell-contact-dependent interactions in liquid and solid media. We combined growth measurements, flow cytometry and fluorescence microscopy to characterize these interactions at both ecological and molecular levels. Our results revealed that *P. aeruginosa* exhibited growth enhancement, inhibition or competitive dominance depending on both the interacting species and the environmental context. Using gene-expression reporters and targeted deletion mutants, we observed that *P. aeruginosa* relied on multiple sensing systems including two-component and quorum sensing systems to modulate their behavior and to optimally respond to competitors. We further found that *P. aeruginosa* deployed tailored responses to each situation. In liquid environments, it primarily invested in iron sequestration through siderophore production, whereas on solid surfaces, it upregulated contact-dependent mechanisms such as the type VI secretion system and type IV pili. Overall, our findings highlight the ability of *P. aeruginosa* to discriminate between competitors and environments through specific sensing and communication systems. This provides new insights into the complexity of bacterial interactions in polymicrobial context and could help in predicting effective therapeutic targets

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Modulation of interbacterial interactions by *Pseudomonas aeruginosa* quorum sensing

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Pseudomonas aeruginosa (Pa), an opportunistic pathogen, frequently coexists with other microorganisms. Pa uses a trio of quorum sensing (QS) systems to regulate the production of some virulence factors. Two of these, the las and rhl systems, involve acyl-homoserine lactone signals; the third, called pqs, primarily uses the signal 2-heptyl-3-hydroxy-4(1H)-quinolone ("PQS"). We are interested in interbacterial interactions that might occur during chronic lung infections, including between Pa and *Stenotrophomonas maltophilia* (Sm), the latter of which has been associated with increased morbidity. We explored Pa and Sm interactions using a co-culture model, where cultures were grown for 24 hours in buffered lysogeny broth. Sm grown in co-culture with Pa co-culture showed 107-fold less colony forming units (CFU) compared to monoculture. We observed that Sm in co-culture with Pa grows for 8 hours and thereafter exhibits a large decline in CFU, demonstrating that Pa is killing Sm. Co-culture of Sm with Pa deficient in las, rhl, or pqs QS resulted in 4-logs greater Sm viability than co-culture with the wildtype. This inhibition was not attributable to las and rhl-regulated toxins that have been previously implicated in competition. Therefore, we interrogated the role of pqs QS and found that co-culture of Sm with a Pa pqsA mutant, which encodes the first enzyme in the PQS biosynthesis pathway, showed similar CFUs to Sm monoculture. Exogenous PQS did not complement this phenotype, suggesting that a quinolone other than PQS is the effector of competition. We found that Sm killing is reduced in competition with a mutant that cannot make the quinolone HQNO; however, other quinolones are also necessary for the full competitive effect. Our work identifies quinolone biosynthesis as a driver for interactions between Pa and Sm and, more generally, suggests a role for pqs QS in modulating interbacterial interactions.

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Relationships between quorum sensing signaling and biofilm development in *Pseudomonas aeruginosa*

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Quorum sensing has long been known to influence biofilm formation in *Pseudomonas aeruginosa*. Here we show production of the major biofilm matrix polysaccharide Psl in *P. aeruginosa* PAO1 is regulated by the quorum regulators LasR and RhIR in stationary-phase cultures. Secretion of Psl into the culture medium requires LasR, RhIR, and the quorum signal molecules N-3-oxo-dodecanoyl-homoserine lactone and N-butanoyl homoserine lactone. Psl production in strains unable to synthesize the homoserine lactone signals can be restored by exogenous introduction of the signal molecules. We found that LasR and RhIR perform different roles in the regulation of Psl production: LasR acts at the promoter of the *psl* operon and activates transcription of the Psl biosynthetic genes, while RhIR activates translation of the *psl* transcripts. Additionally, we demonstrate that quorum sensing and two key secondary messengers, show unexpected spatial activity during the course of biofilm aggregate formation.

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Export by a quorum sensing-controlled drug exporter underlies rifampicin's exceptional activity against strong staphylococcal biofilms

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Biofilm infections on indwelling medical devices are a major cause of healthcare-associated infection and mortality. Most of these infections are caused by staphylococci. The continued clinical challenge with biofilm formation is the association with dramatically increased non-specific antimicrobial resistance. Unlike most antibiotics, rifampicin is active against staphylococcal biofilm infections, however, the mechanism is unknown. Using in vitro assays and mouse models of biofilm infection, we show here that rifampicin is more effective than other antibiotics against staphylococcal agr mutants, which are linked to serious biofilm infections as they produce extended biofilms. We discovered that this superiority is due to an Agr-controlled rifampicin efflux system, making agr mutant biofilms less resistant to rifampicin, rather than more resistant, as to other antibiotics. Our study provides a scientific rationale supporting the use of rifampicin in staphylococcal biofilm infections and emphasizes the importance of understanding genetic adaptations during infection for the use and development of biofilm therapeutics.

"Cell-cell communication in bacteria: new insights and future trends"

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Spatially-resolved bacterial single-cell RNA sequencing links microbe-microbe communication and biofilm functional heterogeneity

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Most microbes inhabit spatially structured communities where interspecies interactions shape gene expression and fitness. Although bacterial transcriptional heterogeneity is thought to drive community-level behaviors and adaptation, it remains poorly understood due to the limitations of bulk transcriptomic approaches. Here, we combined single-cell RNA sequencing (scRNA-seq) with a new analysis framework called Neighborhood Expression Analysis Resolved by sequencing (NEAR-seq) to dissect how interspecies communication influences gene expression heterogeneity in biofilms formed by the oral pathogen *Aggregatibacter actinomycetemcomitans* and the commensal *Streptococcus gordonii*. These species engage in metabolite-mediated communication via *S. gordonii*'s production of the extracellular metabolic cues L-lactate and hydrogen peroxide, which are sensed by *A. actinomycetemcomitans* to modulate its physiology. scRNA-seq revealed distinct *A. actinomycetemcomitans* subpopulations with conserved transcriptional states across mono- and co-culture, while specific subpopulations uniquely upregulated genes linked to microbial interactions and virulence. Notably, *S. gordonii*-induced transcriptional changes in *A. actinomycetemcomitans* were often spatially restricted and heterogeneous, implicating localized microbe-microbe communication in shaping bacterial behavior. Spatial inference via NEAR-seq further connected interspecies organization to altered expression of carbon metabolism and virulence operons. These findings demonstrate that transcriptional heterogeneity, shaped by localized interspecies communication, is a key determinant of bacterial physiology and pathogenic potential in polymicrobial biofilms.

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A systems biology approach to the interaction between *S.cerevisiae* and bacteria in the insect and human gut

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Few studies have examined the genetics lying at the basis of cooperation and competition between strains of *Saccharomyces cerevisiae* and between strains of *S.cerevisiae* and bacteria. Even less studies have carried out this experiments in environmental settings such as inside a grape berry or inside a host. To understand the genetics of ecological interactions, we have used yeast strains from vineyard grapes, insects and bacteria and examined the fitness in single-clone strain cultures of these natural isolates in synthetic wine must (SWM), alone and in presence of lactobacilli. We differentiated fitness according to 3 parameters, 1-growth speed alone and in competition, 2-production of attractive molecules for insects vectoring *S.c.*, 3-induction of tolerogenic or inflammatory responses in the host. We found great differences in the fitness of the eight strains, thus we performed genome- wide analyses in order to identify the genes involved in the establishment of their coexistence in the different environmental conditions. The results highlight the existence of both altruistic and competitive behavior. Regarding the growth rate the altruistic behavior mainly depends on a released heat-shock protein, Hsp12p. The altruistic strain also punishes close relatives non-producers by contact-dependent transmission of a killer toxin, while a membrane protein (Pau5p) can provide resistance against this toxin. The reward–punishment loop created by the combined action of Hsp12p, Pau5p and killer toxin is sufficient to steer a yeast community and ensure the survival of a cooperating strain. Regarding the interaction between yeasts and bacteria the altruistic behavior is observed with lactose as carbon source, where strains of *S.cerevisiae* secrete aminoacids as a reward to lactic acid bacteria that break lactose into glucose and galactose. Finally we show how the ability of *S.cerevisiae* to induce trained immunity or attract insects is totally dependent on the presence of lactic acid bacteria. We conclude that Lactic acid bacteria and yeasts decision on whether to cooperate or compete is strictly dependent on the carbon source available and on specific features of the genomic makeup of the interacting strains.

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RetS serves as a receptor in *Pseudomonas aeruginosa* that senses human-derived molecules

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Bacterial cells employ diverse mechanisms to perceive and respond to host-associated molecules, coordinate intracellular signal transduction, and engage in interkingdom communication. In this study, we demonstrate that the adrenergic antagonist dronedarone (DDR) significantly suppresses quorum sensing (QS) and the pathogenesis in the opportunistic pathogen *Pseudomonas aeruginosa*. Further investigations reveal that DDR specifically targets RetS, a crucial bacterial surface receptor implicated in the repression of the GacS/GacA two-component regulatory system (TCS). Notably, the adrenergic agonist norepinephrine (NE) exerts opposing effects on RetS, thereby reversing DDR-induced phenotypes in *Pseudomonas aeruginosa*. Moreover, we identify the hinge region of RetSDISMED2 as a binding pocket for both NE and DDR, providing insights into the molecular mechanisms underlying their antagonistic effects. It is noteworthy that RetS can directly interact with a diverse array of endogenous metabolites in the human body, thereby modulating the downstream GacS/GacA signaling pathway. Collectively, our findings demonstrate that RetS functions as a receptor capable of broadly sensing human-derived molecules during *Pseudomonas aeruginosa* infection.

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Actions of *Pseudomonas aeruginosa* MvfR/pqsABCDE Quorum Sensing System During Host-Pathogen Interaction

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The mechanism by which *Pseudomonas aeruginosa* (PA) exploits host metabolism to promote immune tolerance and persist in infected hosts remains elusive. One of at least three main quorum sensing (QS) systems in *Pseudomonas aeruginosa* (PA) is the MvfR/PqsABCDE system. In the host, QS can have a profound impact on the ability of PA to establish infections. This QS system, through the global virulence transcriptional regulator MvfR (multiple virulence factor regulator), also referred to as PqsR, controls the synthesis of a range of small molecules, including the 4-hydroxy-2-alkylquinolines (HAQs), 2'-aminoacetophenone (2-AA), and 2-n-heptyl-4-hydroxyquinoline N-oxide (HQNO) that promote virulence, competition, and long-term bacterial presence during infection. We unveiled how this pathogen, through at least one QS signaling molecule, causes distinct metabolic perturbations in macrophages to derange mitochondrial respiration and bioenergetics via the Ppargc1a/Esrra axis and how these alterations drive histone H3 lysine 18 lactylation (H3K18la) in vivo. The H3K18la and consequent transcriptional changes promote PA survival in macrophages. Inhibition of MvfR impedes these immunometabolic and epigenetic changes, thereby reducing PA survival in macrophages. The uncovered QS-driven H3K18la represents a seminal interplay during host-pathogen interaction. Targeting this QS-epigenetic axis may offer a viable therapeutic approach for chronic PA infection.

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Crosstalk in the skin: unraveling the role of *Staphylococcus aureus* in T-cell communication and disease progression in mycosis fungoides

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Mycosis Fungoides (MF) is a rare cutaneous T-cell lymphoma marked by chronic inflammation and complex interactions between malignant T-cells and the skin microenvironment. A striking feature of MF is the frequent colonization of lesional skin by *Staphylococcus aureus*, increasingly recognized not as a passive bystander, but as an active modulator of disease progression. In MF lesions, *S. aureus* reshapes the immune landscape and dominates the microbial community by outcompeting commensals. This dominance is mediated by virulence and immune evasion factors such as Staphylococcal Protein A (Spa), which binds to immunoglobulins and TNF- α receptors and interferes with T-cell signaling. Another key element is the accessory gene regulator (Agr) system, a quorum sensing mechanism that regulates toxin expression, biofilm formation, and immune modulation. We observed that MF-associated *S. aureus* isolates carry different Agr types, indicating diversity in communication systems that may influence virulence and host interaction.

Targeting bacterial communication pathways, including quorum sensing, offers a promising approach to disrupt pathogen signaling and reduce inflammation. Therefore, we are investigating and fractionating bioactive metabolites from fungal sources to modulate bacterial communication and biofilm-associated behavior. Moreover, *S. aureus* isolates from MF patients often show increased antimicrobial resistance and enhanced immune evasion. The pre-existing immune dysregulation in MF creates a niche for stable colonization, while *S. aureus* further impairs host defenses and promotes persistent inflammation that may contribute to tumor progression.

Our study focuses on the molecular dialogue between *S. aureus* and malignant T-cells, aiming to elucidate how bacterial signaling affects host cell behavior. By linking the genetic traits of *S. aureus* isolates to their interaction potential, we seek to identify microbial factors driving immune dysregulation, chronic inflammation, and disease progression.

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The Chemical Language of the Gut-Brain Axis: Pyrazinone Signaling in Microbiota-Host Interactions

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Human gut microbiota plays a crucial role in host immunity, nutrition, and behavior, largely through quorum sensing (QS), a process in which bacteria coordinate collective behaviors by producing and detecting extracellular signaling molecules. Recently, a novel class of bacterial QS molecules, pyrazinones, has been identified as mediators of microbial communication and virulence regulation in intestinal pathogens. Intriguingly, some bacterial QS receptors for pyrazinones also respond to host-derived neurotransmitters, suggesting a potential link between microbial signaling and host neurophysiology.

We hypothesize that gut microbiota-derived pyrazinones interact with host neurotransmitter receptors, influencing both the enteric and central nervous system function and ultimately modulating host behavior. Despite the prevalence of pyrazinone synthase homologs in gut commensals, no pyrazinone host receptors have been identified.

To address this gap, we will employ advanced untargeted metabolomics to characterize the structural diversity of microbiota-derived pyrazinones and validate their identities through chemical synthesis. To identify host receptors, we will use Activity-Based Protein Profiling (ABPP) with synthetic pyrazinone probes to covalently label receptor proteins in intestinal and neural cell models. By elucidating the molecular mechanisms underlying pyrazinone-mediated gut-brain interactions, this research will provide critical insights into microbiota-host communication and its potential role in modulating complex behaviors.

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Cutting off communication: a chemical approach to blocking bacterial pathogenesis

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In *Vibrio* species, quorum sensing signaling culminates in the production of the master transcription factor SmcR that regulates group behavior genes in a density-dependent manner. SmcR family proteins were discovered in the 1990s as central regulators of quorum sensing gene expression and later discovered to be conserved in all studied *Vibrio* species. SmcR homologs regulate a wide range of genes involved in pathogenesis, including but not limited to genes involved in biofilm production and toxin secretion. As archetypal members of the broad class of TetR-type transcription factors, each SmcR type protein has a predicted ligand binding pocket. However, no ligand has been identified for these proteins that control their function as regulators. Previously, we identified a suite of small molecule thiophenesulfonamide inhibitors that act as 'anti-virulence' therapeutics that target the SmcR family of proteins and block activity in vivo but do not kill the cells. Here, we sought to identify the mechanism of action of these compounds and focused on our lead molecule, PTSP. We used structure-function analyses to identify eight PTSP-interacting residues in the ligand binding pocket that are required for PTSP inhibition of *Vibrio vulnificus* SmcR. Binding of PTSP to SmcR drives allosteric unfolding of the N-terminal DNA-binding domain and, in this state, SmcR is degraded by the ClpAP protease. SmcR degradation controls the timing of the phenotypic switch between high and low cell density, and strains expressing degradation-resistant smcR alleles are impervious to changes in cell density state. These studies implicate ligand binding as a mediator of SmcR protein stability and function, which dictates the timing of quorum sensing gene expression in three *Vibrio* pathogens.

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Synthetic chemical strategies to understand, alter, and divert bacterial communication pathways

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Our research is broadly focused on the design, synthesis, and application of non-native ligands that can intercept bacterial quorum sensing and provide new insights into its biochemical mechanisms and its roles in host/microbe interactions and the environment. At high cell densities, many common bacteria use quorum sensing to switch from a single cell existence to that of a multicellular community. This lifestyle switch is significant; only in groups will pathogenic bacteria turn on virulence pathways and grow into impervious communities called biofilms that are the bases of chronic biofouling and infections. We have developed a range of non-native compounds that can block or activate quorum sensing pathways, some with high selectivities, potencies, and chemical stabilities, in both Gram-negative and Gram-positive bacteria. These small molecules and peptides provide an approach to study quorum sensing with both spatial and temporal control in a range of biologically relevant settings. We have applied our chemical tools in vitro and in vivo to investigate quorum sensing as an anti-infective target. Ongoing work is focused on understanding their molecular interactions with key protein receptors involved in quorum sensing pathways, with native signals, and with membranes. In this presentation, I will introduce my lab's research approach and highlight our most recent results.

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Exploring indole signaling as a target for antivirulence therapy against enterotoxigenic *Escherichia coli* (ETEC)

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Indole signaling is being explored as one of the promising targets for antivirulence therapy against antibiotic-resistant pathogens. Indole has been reported to influence key virulence-related phenotypes, particularly motility and biofilm formation, in various bacterial pathogens. This study aimed to investigate the impact of indole and its analogues on enterotoxigenic *Escherichia coli* (ETEC). The results revealed that indole decreased both swimming motility and biofilm formation in ETEC across concentrations ranging from 100 μM to 1000 μM , with a maximum reduction of 75% in swimming motility and 47% in biofilm formation at the highest concentration, compared to untreated cultures. RT-qPCR showed that flagellar genes were downregulated by 3.3-fold and also revealed decreased expression of the heat-stable enterotoxin by 2.7-fold. Finally, indole decreased the virulence of ETEC in the invertebrate infection model *Galleria melonella*, resulting in increased larval survival by 2.4-fold, compared to the untreated group. 29 indole analogues selected based on previous work with vibrios, were screened to explore the antivirulence potential further. 16 of these analogues were selected for further experiments, of which 9 were found to decrease virulence. At 500 μM , 4-fluoroindole, 5-fluoroindole, 6-fluoroindole, 7-chloroindole, and 7-iodoindole decreased swimming motility by 84%, 87%, 90%, 89%, and 96%, respectively, compared to the control. Regarding biofilm formation, 4-fluoroindole caused a 61% reduction, while 7-bromoindole, 7-bromoindole-2-carboxylic acid, and indole-3-acetonitrile exhibited effects similar to indole. These findings indicate that indole signaling controls ETEC virulence, and that indole analogues—some of which have more potential than indole itself—show promise in applications aiming for alternative biocontrol approaches for antibiotic-resistant pathogens.

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The over-expression of the *Pseudomonas aeruginosa* phnAB operon abrogates its pyocyanin production possibly by interfering with PqsE expression at the post-transcriptional level

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The production of several *Pseudomonas aeruginosa* virulence-associated traits is regulated at the transcriptional level by a complex quorum-sensing response comprising 3 receptor-signal systems hierarchically arranged: The LasR/3-oxo-dodecanoyl homoserine lactone (3O-C12-HSL) produced by the LasI enzyme, at the top of the hierarchy, activates the expression of the second system constituted by RhlR and butanoyl homoserine lactone (C4-HSL) produced by RhlI, and the PqsR transcriptional regulator which is the receptor of the third system. In turn, PqsR when coupled with the alkyl-quinolones 4-hydroxy-2-heptylquinoline (HHQ) or 2-heptyl-3,4-dihydroxyquinoline (PQS), activates transcription of the pqsABCDE operon. The first four genes of this operon produce HHQ, which is converted to PQS by PqsH, while PqsE forms a complex with RhlR that is required for the transcription of genes involved in the production of the toxin pyocyanin (phzABCDEFG operons), a crucial virulence factor. RhlR and C4-HSL activate the rhlAB operon which encodes enzymes that synthesize virulence-related biosurfactant rhamnolipids. Compounds that block the activity of LasR, PqsR or PqsE are actively sought as alternative therapies to inhibit *P. aeruginosa* virulence. Downstream of the pqsABCDE operon, the PqsR/PQS or PqsR/HHQ regulated phnAB operon encodes an anthranilate synthase that produces the precursor of HHQ synthesis. We found that over-expression from a plasmid of the phnAB operon abolished pyocyanin production in the PAO1 strain, while significantly reducing it in several *P. aeruginosa* clinical and environmental isolates. Using PAO1 as a model to unravel the molecular mechanism involved in the abrogation of pyocyanin production by the over-expression of the phnAB operon we have learned that (1) it is not related to the production of anthranilate since adding it to the culture medium does not affect pyocyanin production, and (2) that Rhamnolipid production is not much reduced, ruling out phnAB over-expression affecting RhlR/C4-HSL. We found that the effect of phnAB over-expression in pyocyanin production is at the transcriptional level of the phzABCDEFG1 operon, and reduced transcription of this operon does not involve LasR or RsaL repression, and that PAO1 with the phnAB-plasmid produces HHQ and PQS, showing that the pqsABCD genes are expressed. Additionally, we showed that pqsE transcription is unaffected. These findings suggest that the PqsE protein is involved in the abrogation of pyocyanin production and that its level is reduced when phnAB operon is over-expressed. We are in the process of determining PqsE levels in the presence and absence of the phnAB-plasmid. Understanding the molecular mechanism of pyocyanin abrogation by the over-expression of the phnAB operon will shed light on an additional point of regulation of the quorum sensing response of this important opportunistic pathogen that might be useful for developing anti-virulence therapeutic strategies.

Quorum sensing coordinates a multi-layered phage defense strategy in *Vibrio alginolyticus*

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Bacteriophages are ubiquitous predators of bacteria, shaping microbial diversity and evolution. While receptor-based resistance is well characterized, the regulatory integration of surface and intracellular defense mechanisms remains poorly understood. Here, we uncover a quorum-sensing-induced, multilayered phage defense strategy in the marine pathogen *Vibrio alginolyticus*.

At high cell density, quorum sensing represses expression of the phage receptor, reducing adsorption of the broad-host-range phage KVP40. Simultaneously, a novel intracellular defense system encoded within a genomic island is activated by the combined signals of quorum sensing and phage infection. Mutants locked in low-cell-density (Δ hapR) or high-cell-density (Δ luxO) states, along with physiological assays using cell-free supernatants, reveal that receptor repression and intracellular defense are tightly coordinated by quorum sensing. Through comparative genomics and functional assays, we identify a four-gene operon within the larger genomic island as essential for phage resistance. Intriguingly, this operon forms a 4.5 kb circularizable DNA element that excises independently of phage infection and appears in sequencing data across the *Vibrio* genus as an extrachromosomal element. This circularization, validated by PCR and sequencing, suggests a modular and potentially mobile defense architecture.

Our findings demonstrate that quorum sensing not only modulates surface-level phage susceptibility but also governs the activation of a previously uncharacterized, mobile defense element. This dual-layered strategy may enable *V. alginolyticus* to dynamically balance phage resistance with fitness costs, offering new insights into how quorum sensing coordinates microbial survival strategies in marine environments.

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Microbial quorum sensing signals, secrets and sabotage

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Understanding how microbes communicate with each other and with their environment is fundamental to deciphering microbial behaviour in complex ecosystems. Quorum sensing (QS) signalling mechanisms have emerged as central players in regulating collective bacterial activities, from the expression of virulence factors to biofilm resilience and interkingdom interactions with hosts such as plants, algae and humans.

A major focus of our research has been to understand the mechanisms of QS signal sensing and transduction in *Pseudomonas aeruginosa*, and to exploit these pathways for the development of therapeutic interventions and diagnostics. This lecture will highlight some of the successes, frustrations, and future directions in this evolving field.

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Revealing New Links Between the Antibiotic Resistance Gene *aph* and Virulence in *Pseudomonas aeruginosa*

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Pseudomonas aeruginosa utilises intricate intracellular and intercellular signalling systems to adapt to environmental changes, regulate virulence, and coordinate social behaviours. It also harbours various antimicrobial resistance mechanisms, making infections difficult to treat. One such mechanism is mediated by the chromosomal *aph* gene, which confers intrinsic resistance to kanamycin and related aminoglycosides. However, potential functions of *aph* beyond conferring antibiotic resistance have remained unexplored.

In this study, we reveal potential metabolic roles for *aph*, linking it to intracellular signalling via the second messenger c-di-GMP. Our data suggest that *aph* expression may be modulated by intracellular c-di-GMP levels and, in turn, may indirectly affect phenotypes such as motility and biofilm development.

The transcriptional analysis revealed that *aph* significantly affects the mRNA levels of major virulence genes in *P. aeruginosa*, potentially contributing to host damage. Among 83 differentially regulated genes, 69 were found to be upregulated by the overexpression of *aph*. Most of these differentially expressed genes belong to iron-associated processes, pyoverdine biosynthesis, and biofilm formation, processes tightly linked to quorum sensing and virulence. These findings were validated by RT-qPCR, lux-based reporter constructs, and phenotypic assays. Together, our findings indicate that *aph*, beyond encoding an aminoglycoside-modifying enzyme, may contribute to the pathogenicity of *P. aeruginosa* by interacting with signalling pathways. Understanding this dual role may enable the development of specific inhibitors targeting *aph*-linked virulence regulation, ultimately enhancing the therapeutic potential of kanamycin-class antibiotics in treating *P. aeruginosa* infections.

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Secondary metabolites, Fe and sugars: the multifactorial antagonism between *Bacillus subtilis* and *Pseudomonas protegens*.

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Several bacterial species found in association with plant roots, such as *Bacillus subtilis* and *Pseudomonas protegens*, display beneficial activity for their host. However, these genera rarely cooperate, which hampers the development of a biofertilizing bacterial consortium involving these two species. When inoculated together on roots, *P. protegens* outcompetes *B. subtilis* and hinders its ability to associate with the plant. Side-by-side colonies on solid media revealed that, under certain conditions, the presence of *P. protegens* led to the secretion of pulcherriminic acid (PA) by *B. subtilis*. This chelator precipitates upon binding to Fe, thereby sequestering it and preventing the production of reactive oxygen species. We hypothesized that this interaction is mediated by secondary metabolites, given the physical separation of the two colonies. First, we determined that only certain strains within the *P. fluorescens* clade could trigger PA production. Comparative genomic analysis was unable to identify specific genes involved due to the high homology between strains and the difficulty in establishing a threshold. Importantly, induction of PA was dependent on the *Pseudomonas* GacA-GacS system, which controls the production of multiple secondary metabolites. At least two metabolites or proteins appeared to trigger PA production by *B. subtilis*: a volatile compound, identified as hydrogen cyanide, and a yet-to-be-determined molecule under the control of the VgrG1B cluster, which is associated with the T6SS. Intriguingly, the T6SS itself was not involved in the interaction. Finally, the environmental nutritional conditions have a significant impact on the interaction, as the outcome is significantly different depending on the carbon source available. In conclusion, the interaction between *B. subtilis* and *P. protegens* is multifactorial and dependent on the environmental conditions. Our observations suggest that the nature of bacteria-bacteria interactions should be viewed as dynamic, rather than categorized as beneficial or antagonistic.

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Light-driven selection and metabolic potential of a purple phototropic bacterial consortium cultivated on dairy waste: implications for microbial communication and biostimulant activity

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In natural environments, purple phototrophic bacteria (PPB) exhibit remarkable metabolic plasticity and social-like behavior in response to environmental stimuli. Here, we present an in-depth study of a light-responsive PPB consortium enriched on a dairy industry by-product and cultivated in a photobioreactor (PBR) under monochromatic light intensities (10-60 W/m²). Community analysis revealed a distinct shift in dominant genera: *Rhodopseudomonas* prevailed under low light, while *Rhodobacter* dominated at higher intensities. Despite these dynamics, PPBs maintained a relative abundance >75% across all conditions, indicating robust consortium stability. To further investigate microbial interactions and spatial differentiation, we sampled the photobioreactor at multiple time points and growth phases for metagenomic analysis. Special attention was given to the biofilm formed on internal surfaces during continuous operation. Our goal was to assess whether the biofilm was dominated by a single taxon or reflected a more complex microbial architecture, and how this structure evolved compared to the initial, more homogeneous state.

Subsequently, we isolated and sequenced axenic representatives of the two dominant strains (*Rhodopseudomonas palustris* and *Rhodobacter capsulatus*), which together represented ~80% of the community diversity. Hybrid genome assemblies using long and short raw reads, revealed for both strains conserved pathways for phototrophy (CO₂ fixation), nitrogen fixation (*nifHDK* operon), and, notably, the biosynthetic potential for 5-aminolevulinic acid (5-ALA), a compound with established plant biostimulant properties.

These findings suggest that, in photobioreactor conditions, light not only shapes microbial community structure but may also influence interspecies interactions and cooperative metabolite production. Ongoing kinetic experiments with pure and co-cultures aim to quantify 5-ALA yields and support the development of model-guided strategies for optimizing its production. Overall, this work illustrates the potential of phototrophic microbial consortia for sustainable biotechnological applications and raises compelling questions about quorum sensing and signaling in microbiomes.

"Cell-cell communication in bacteria: new insights and future trends"

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Investigation of microbiota-mucus-host interactions within an engineered colonic simulator

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The gut microbiota and the interaction with the mucosal layer that covers the epithelium play a fundamental role in shaping microbial spatial organisation, behaviour, and metabolite production. However, the limitations of current in vitro models present a challenge to deepening our understanding microbial dynamics in a physiologically representative context. Using a previously described triple-staged colonic microbiome model, we developed a mucus biomimetic by using a PEG crosslinker with purified pig gastric mucin. This biomimetic mucus was coated onto sampling support structures and compared with mucin/agar coated or uncoated structures. Spatial-temporal analysis was conducted on the biofilms formed in the proximal vessel and distal vessel up to 10 days after inoculation. Mucus-associated bacterial populations were quantified using qPCR, biofilm structures were visualised with SEM, and untargeted metabolomics analysis was performed. Our results showed a significant increase in biofilm formation on mucus-coated surfaces compared to the controls, particularly species known to colonise the colonic mucosa in-vivo. *Akkermansia* levels were increased on the mucus biofilm vs mucin/agar or uncoated by 1.3- and 0.87- log₁₀ CFU/mL, respectively. Similarly, *Bacteroides* (2.26- and 2.36 log₁₀ CFU/mL, respectively) and *Bifidobacterium* (1.34- and 1.24 log₁₀ CFU/mL respectively). The SEM images revealed the biofilm structural stability over time highlighting the ability of mucus in promoting bacterial adhesion and colonisation in the colonic environment. Bile acid analysis using untargeted LC-MS revealed greater microbial metabolism of primary and secondary bile acids within the biomimetic mucus-associated biofilm.

Our mucus biomimetic supported the growth of known mucus-dwelling microbes for an extended time compared with mucin/agar and uncoated controls. Taken together, this supports the use of a mucus biomimetic to accurately model mucus-associated populations in vitro.

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Targeting the *Pseudomonas aeruginosa* las quorum-sensing system with a pyridine-based thiazolyl-hydrazone to prevent biofilm-associated infections

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Background: *Pseudomonas aeruginosa* are highly recalcitrant to antibiotic treatment and are often associated with chronic diseases in immunocompromised patients. Quorum sensing (QS) is the key regulator of *P. aeruginosa* pathogenicity and virulence, with the las system playing a central role in biofilm development and virulence control. Despite extensive research, many previously identified QS inhibitors, such as furanones, have not found clinical application due to their low bioavailability and high toxicity. In this study, the potential of a novel pyridine-based thiazolyl-hydrazone (TTNF37) to interfere with the las QS system and prevent biofilm formation in *P. aeruginosa* was investigated.

Methods: The effect of TTNF37 on the las system was assessed using *P. aeruginosa* bioreporter strains (R3 and PA14 wild type) and bioluminescence-based assays. Biofilm formation interference was evaluated by quantifying biomass, culturability, and metabolic activity.

Results: TTNF37 suppressed las QS system dependent bioluminescence in a concentration-dependent manner, with reductions ranging from 26% to 98%. Moreover, the tested pyridine-based thiazolyl-hydrazone impaired both the production and detection of the 3-oxo-C12-HSL autoinducer, resulting in 56% and 65% reductions in bioluminescence, respectively. At 1000 µg mL⁻¹, TTNF37 reduced the biomass by 50%. In addition, metabolic activity was reduced by 38% and culturability was reduced by 1.55 log (CFU mL⁻¹) using TTNF37 at 100 µg mL⁻¹.

Conclusion: TTNF37 acts as a potent las QS inhibitor and effectively prevents biofilm formation by reducing biomass, metabolic activity, and culturability. This new hybrid scaffold highlights the potential of pyridine-based thiazolyl-hydrazones as promising antipathogenic and antivirulence agents for the prevention and treatment of *P. aeruginosa* biofilm-associated infections.

Keywords: Antibacterial resistance, biofilm prevention, quorum-sensing inhibition, *Pseudomonas aeruginosa*, thiazolyl-hydrazone.

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In situ activation of a synthetic quorum sensing circuit in *Escherichia coli* colonizing the gut of *Caenorhabditis elegans*

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Synthetic biology offers powerful tools to program bacterial behavior through engineered gene circuits. Among these, quorum-sensing-based systems have been widely explored for coordinating gene expression at the population level. However, applying such systems in vivo within host-associated microbiotas remains challenging, particularly in simple animal models where spatial and temporal control of gene expression is critical. Here, we present a proof-of-concept study demonstrating in situ activation of a synthetic quorum sensing circuit in *Escherichia coli* BW25113 colonizing the gut of the nematode *Caenorhabditis elegans*. We engineered two *E. coli* strains: a Sender strain carrying the *lasI* gene from *Pseudomonas aeruginosa* under control of the arabinose-inducible PBAD promoter, and a Receiver strain expressing red fluorescent protein (RFP) under control of the *Plas* promoter, which is activated by the LasR protein in the presence of the autoinducer 3-oxo-C12-HSL. These strains were designed to communicate through AHL production, allowing population-level signal propagation and gene expression. Worms were fed different proportions of Sender and Receiver strains over 5 days to enable intestinal colonization. Subsequently, they were washed, transferred to M9 buffer containing arabinose, and maintained for 3 hours. Fluorescence microscopy revealed robust RFP expression in the intestines of worms exposed to arabinose, consistent with in situ activation of the quorum sensing circuit. No significant fluorescence was observed in control groups lacking either arabinose or sender strains. These results confirm that the Sender bacteria successfully produced the AHL signal in response to the inducer. The Receiver bacteria residing in the same host environment detected the signal and responded by expressing RFP. To our knowledge, this is the first demonstration of an inducible cell-cell communication circuit functioning in situ within the gut microbiota of *C. elegans*. This platform provides a tractable model to study bacterial communication, spatial signal propagation, and host-microbiota interactions under controlled conditions. Ongoing experiments explore how circuit activation influences host physiology or microbial community dynamics. This work highlights *C. elegans* as a powerful in vivo model for testing synthetic genetic circuits in complex biological contexts, paving the way for future microbiome engineering, biosensing, and therapeutics applications.

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Interspecies induction of biofilm development in *Bacillus subtilis*

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Plants engage closely with a diverse community of microorganisms present in their vicinity. Among plant-associated bacteria, *Bacillus subtilis* is well-known for its ability to form biofilms that facilitate root colonization, promote plant growth, cycle nutrients, and defend against pathogens. The formation of these biofilms represents a complex biological system characterized by intricate processes and interactions that remain largely enigmatic. Notably, *B. subtilis* biofilm formation is influenced by secondary metabolites produced by soil-derived bacterial isolates. Our research group has collected 121 spore-forming Bacillales strains from diverse habitats across the globe, a taxonomic group that is recognized for its capacity to produce various secondary metabolites. This study aims to identify chemical signaling molecules from these isolates that influence gene expression related to *B. subtilis* biofilm development, specifically focusing on *eps* operon that is required for extracellular polysaccharide production. Based on LC-MS analyses and bioactivity assays of the individual nanofractions, we discovered that *Bacillus altitudinis* produces amicoumacin compounds induce the expression of biofilm-related gene, *eps*. Isolates close related to *B. altitudinis* display different level of activation of biofilm gene expression, suggesting diversity in amicoumacin-like metabolite production in these isolates. Additionally, we revealed that mutations in *kinB* or *yerH* genes, encoding a sensor kinase and lipoprotein, respectively, alter amicoumacin-mediated promotion of *eps* expression in *B. subtilis*. Our ongoing transcriptome experiments elucidate the gene regulatory pathways involved in signal perception in order to leverage the knowledge about cross-species communication signals towards enhancing the plant-promoting properties of *B. subtilis*.

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Different combinations of strains from a phytopathogenic microbial consortium result in the induction or repression of pathogenic activity.

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Agaves thrive in extreme heat and drought, particularly in semi-arid regions. Agave salmiana is used to keep soil and humidity in agricultural lands, for soil restoration, as cattle feed, and to produce spirits, fibers, and traditional foods. Both *A. salmiana* plantations and wild agaves are affected by insect plagues and diseases. Plant diseases are often attributed to a single species; however, many diseases result from multispecies consortia. We isolated a natural consortium of two bacteria and six fungi from a grey spot lesion of *A. salmiana*, which were identified using metagenomics (amplicon or whole DNA metagenomic sequencing). The pathogenicity of single strains and consortia was evaluated by measuring the area of the lesion produced when inoculated into Braeburn apples. Induction or repression was calculated as the ratio of the area of the lesion of the consortium to the sum of the areas of the individual members. *Pantoea endophytica* and *Penicillium* sp. were nonpathogenic, while *Aspergillus* sp. was the most pathogenic. Notably, the consortium caused a smaller lesion area than the *Aspergillus* strain, i.e., the interaction of this fungus with the other members decreased its pathogenicity. In most synthetic consortia, pathogenicity was restricted; however, in the consortium of the two *Alternaria* sp. strains, it increased by a factor of two. The interaction networks indicate that, in most cases, the interactions were negative in terms of pathogenicity. *P. endophytica* inhibits the pathogenicity of *Fusarium* sp. strain H-6 and *Aspergillus* sp. Currently, we are building each strain's genome from massive metagenomic sequences to complete the taxonomy, obtain functional information, and hypothesize possible interaction mechanisms. At the same time, we are conducting in vitro bioassays to assess these interactions further. Our results indicate that in consortia, phytopathogenicity can be induced or repressed depending on the members, and this opens the door to using consortia for controlling phytopathogens.

Key words: Phytopathogenic consortium, inter-kingdom consortia, Agave salmiana, pathogenicity induction, pathogenicity repression.

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Bacterial interactions in traditional milpa agroecosystems at a community level

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Microbial interactions are key driving forces of ecological complexity and biodiversity. At the cellular level, many mechanisms have been described for both positive and antagonistic interactions. These advances offer mechanistic explanations for the observable impacts of microbial populations on those of other strains. Therefore, microbial interactions are likely to produce patterns of co-occurrence (where the abundance of populations of interacting strains is positively correlated) and exclusions (where the abundance is negatively correlated). Some of these correlations can be spurious and explained by random coincidence or underlying causal variables, such as pairs of strains having similar niches. Nevertheless, the study of microbial co-occurrence and exclusion patterns at a community level is still likely to inform about actual interactions in natural environments. In soil communities, understanding the correlation structure of microbial populations can contribute to our understanding of the abundance patterns of key microorganisms that drive soil processes. In this regard, traditional agroecosystems are of particular interest, as microbial interactions could play a role in sustainable agriculture. Milpa agroecosystems are small-scale agricultural systems, which have been cultivated for millennia in Mesoamerica. We sampled milpa soils at a regional scale, in a diverse cultural, climatic, and vegetation gradient. We used shotgun metagenomics to estimate the abundances of microbial populations directly from the environment and calculated the correlation structure of all bacteria. We found that negative correlations were more common between strains from different phyla than within the same phylum. Actinobacterial strains exhibited extensive negative correlations with those from most other abundant phyla, including Pseudomonadota, Acidobacteriota, Planctomycetota, Bacteroidota, and Verrucomicrobiota, but not with those from Chloroflexota. On the contrary, positive correlations were much more common within phyla. These results suggest that, in milpa soil microbial communities, both positive and negative interactions influence community structure and may contribute to the abundance patterns of many bacteria.

Keywords: Community-level interactions, traditional agroecosystems, metagenomics, cooccurrence networks.

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Unraveling the potential of Quorum Sensing inter-species dialogue to restore microbiota's community dynamics

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Bacterial members of the gut microbiota community are important for many aspects of host health. Antibiotics can induce microbiota imbalances, with negative consequences for the host (dysbiosis). Here we will utilise microbial interactions mediated by quorum sensing (QS) to tackle gut dysbiosis caused by antibiotics. We are testing whether a next-generation probiotic, isolated by our group, favors re-establishment of gut microbiota through native QS signals with benefits for the host. QS is a cell-to-cell mechanism allowing bacteria to engage in group behavior via exchange of chemical signals. These molecules such as Autoinducer-2 (AI-2) activate signaling cascades in bacterial populations to synchronize genes involved in various group behaviors.

We have recently discovered a novel murine-isolated non-pneumoniae commensal *Klebsiella* sp. ARO112 which provides colonization resistance against multiple intestinal pathobionts and promotes recovery of butyrate levels and butyrate-producing bacteria after antibiotic-induced dysbiosis. The low pathogenicity of this strain and its *luxS* gene allow QS molecule production. We hypothesize that ,after dysbiosis, ARO112 drives overall transcriptomic response via production and secretion of AI-2 molecules, forcing the bacteria to engage in QS, thus significantly increasing the Bacillota/Bacteroidota ratio, and promoting community restoration. Moreover, we hypothesized that the QS manipulation, through the restoration of the bacterial inter-species dialogue, will reduce the microbiota imbalance, and the gut inflammation caused by antibiotic use. To influence the QS dialogue, we have constructed a combination of ARO112 mutants, with high AI-2 production or high AI-2 uptake from the environment, allowing us to manipulate the QS signals. Moreover, CRISPR/Cas9 was used to insert a GFP-coding gene within a pseudogene allowing us to follow the long-term colonization ability of these mutants in the murine gut. Preliminary data show that the QS signals, released by ARO112, favor the restoration of the Bacillota phylum, particularly favoring a higher relative abundance of multiple key butyrate-producing families (Lachnospiraceae, Butyricicoccaceae, Oscillospiraceae, Ruminococcaceae) after antibiotic-induced dysbiosis, in SPF mice.

To explore the possible beneficial consequences of these changes at the host level, we aim to determine the effects of ARO112-produced AI-2 on the ratio of crucial host immune cell populations present in the colon, as well as on the levels of pro-inflammatory cytokines, using FACS.

We expect that this ongoing project will provide key mechanistic comprehension of the QS signaling mechanism in microbiota communities and unravel the potential of this newly discovered next-generation probiotic to promote microbiota dynamics through the restoration of bacteria-bacteria communication after antibiotic treatment.

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Cell-Cell Communication in *Pseudomonas corrugata*: A LuxR-Mediated Hierarchical System Regulates the Production of Bioactive Cyclic Lipopeptides

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Pseudomonas corrugata, a ubiquitous bacterium belonging to the *P. fluorescens* group (*P. corrugata* subgroup), is known as the causal agent of tomato pith necrosis (TPN), yet also acts as a biocontrol agent against several plant pathogens. These biological functions are largely attributed to the production of the bioactive cyclic lipopeptides (CLPs) corpeptins and cormycin. Strains from this taxon also harbor a conserved N-acyl-homoserine lactone (AHL) quorum sensing (QS) system, PcoI/PcoR. Both the CLP biosynthetic and QS genes are located within a large genomic island that is widespread in the subgroup. In our model strain CFBP 5454, CLP production is regulated by the PcoI/PcoR QS system, where the PcoR-AHL complex activates pcoI and the co-transcribed rfiA. RfiA, a LuxR-type regulator lacking an autoinducer-binding domain, acts downstream to modulate CLP biosynthesis. The analysis of mutants for corpeptins biosynthesis and transport genes revealed they retained cormycin production and still exhibited phytotoxic and antimicrobial activity. However, the specific contribution of cormycin to these phenotypes had not been yet investigated. To address this gap, we constructed a mutant strain (PCOCRMA) with a deletion in crmA, a putative cormycin biosynthetic gene. Mass spectrometry confirmed no production of cormycin in PCOCRMA. Phenotypic assays demonstrated that regulatory mutants and PCOCRMA exhibited reduced or abolished production of one or both CLPs, along with associated phenotypic changes. Notably, PCOCRMA displayed significantly diminished antifungal activity and phytotoxicity, underscoring cormycin's key role in these traits. These findings suggest a hierarchical PcoR-RfiA regulatory cascade governing cormycin production while revealing that environmental factors (i.e. temperature and nutrient availability) can regulate its biosynthesis. Furthermore, the observation that fluorescent pseudomonads isolated from TPN—harboring the CLP-QS genomic island—can activate *P. corrugata* QS system highlights the pivotal role of cell-cell communication and CLP production in *Pseudomonas* interactions within the rhizosphere and in complex diseases including TPN.

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Quorum sensing-mediated rhamnolipid production prevents biofilm formation of *Pseudomonas aeruginosa* on anti-attachment micro-topographies

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The development of non-leachable bio-instructive materials that inhibit bacterial biofilm formation offers a promising alternative strategy to reduce infection. This requires a better mechanistic understanding of bacteria-surface interactions from the perspective of both the bacterium and the nature of the surface. Relationships between cellular responses to materials and their properties are still poorly understood, preventing reliable prediction and design of improved materials. Here, we investigate the mechanisms by which bacteria sense and respond to previously identified pro- and anti-attachment topographies.

Pseudomonas aeruginosa produces rhamnolipid biosurfactants that contribute to surface migration, quorum sensing (QS) signal molecule solubilization, and biofilm maturation and dispersal. They also act as anti-adhesives. We therefore investigated whether exogenous provision of purified rhamnolipids or abolition of their biosynthesis by mutation of the *rhlA* gene influenced biofilm formation on pro- and anti-attachment topographies. Rhamnolipids are regulated via QS and in particular via the *rhl* QS system comprising the transcriptional regulator *RhlR* and the *RhlI*-generated QS signal molecule, N-butanoyl-homoserine lactone (C4-HSL). Therefore, we evaluated the biofilm phenotype of a *rhlI* mutant that is unable to synthesize rhamnolipids since C4-HSL signal molecule biosynthesis is abolished.

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The Effects of Natural and Environmental Metabolites on Quorum Sensing in *Pseudomonas aeruginosa*

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Bacterial populations use quorum sensing (QS) to regulate gene expression and behaviors essential for survival and pathogenicity.

This study explores two approaches targeting *P. aeruginosa* QS systems through natural metabolites, investigating the effects of ginger plants and environmental cyanobacteria on this opportunistic pathogen. In addition to standard bioassays we also apply untargeted metabolomics analyses to evaluate changes in bacterial virulence.

P. aeruginosa utilizes QS mechanisms to regulate virulence and biofilm formation, which are key factors in a wide range of human infections. Inhibition of QS signaling can attenuate pathogenicity. The known medicinal properties of ginger prompted investigation into its effects on *P. aeruginosa* QS systems. Natural ginger-derived compounds, including paradol, shogaol, and their analogs, were synthesized and were shown to inhibit the Las and PQS systems, as well as reduce virulence factor production.

Cyanobacteria are known to produce a variety of bioactive metabolites, some of which may possess antibacterial or antiviral activity. Understanding their interactions with *P. aeruginosa* could contribute to a deeper understanding of microbial communication. This study aims to explore the potential effects of cyanobacterial compounds on quorum sensing (QS) systems and related microbial behaviors.

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Temperature-sensitive control of RhIR links environmental cues to quorum sensing in *Pseudomonas aeruginosa*

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The versatile bacterium *Pseudomonas aeruginosa* thrives in a wide range of environments and is well known for its role as an opportunistic pathogen. In line with this adaptability, *P. aeruginosa* produces various exoproducts essential for survival and virulence, many of which are regulated through quorum sensing (QS). These factors are also modulated in response to environmental cues, such as temperature shifts. As an opportunistic pathogen, *P. aeruginosa* is generally believed to activate its virulence factors at host-like, warm-blooded temperatures rather than at environmental temperatures.

Recent studies elucidated the functional structure of the QS transcriptional regulator RhIR, whose activity depends on its cognate autoinducer N-butanoyl-L-homoserine lactone (C4-HSL) and the moonlighting chaperone PqsE. Given the impact of temperature on biomolecular dynamics, we examined how temperature influences RhIR activity using the RhIR-regulated *phzA1* promoter as a proxy. Unexpectedly, RhIR activity was higher at 25°C than at 37°C. This temperature-dependent effect appears to stem from changes in RhIR turnover: the presence of PqsE boosts RhIR activity at 37°C nearly tenfold, reaching levels similar to those observed at 25°C. This lower, environmental-like temperature promotes increased affinity between RhIR and C4-HSL, a trait significantly compromised in the absence of PqsE.

The observation that RhIR is more active at 25°C than 37°C is also supported by the increased transcription at 25°C of other RhIR-regulated genes such as *phzA2* and *azeB*, though not *rhIA*. These results suggest that this response depends on the structural integrity of the complex, indicating that temperature functions as an additional regulating and stabilizing factor of RhIR function.

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PqsE is a conserved and functionally critical component of the *Pseudomonas aeruginosa* quorum sensing network

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Pseudomonas aeruginosa is an opportunistic pathogen implicated in numerous acute and chronic infections. The expression of many of its virulence factors is tightly controlled by three interconnected quorum sensing (QS) systems: *las*, *rhl*, and *pqs*. The *pqs* system utilizes 4-hydroxy-2-alkylquinolines (HAQs) as signaling molecules to activate the transcriptional regulator MvfR (PqsR), which in turn induces HAQ production through the *pqsABCDE* operon. The final gene in this operon encodes PqsE, a multifunctional protein. In addition to its role as a thioesterase in HAQ biosynthesis, PqsE enhances the stability of RhIR—the transcriptional regulator of the *rhl* system—thus promoting the regulation of virulence-associated genes.

Due to its central role in pathogenesis, PqsE is considered a promising therapeutic target for *P. aeruginosa* infections. While its interaction with the RhIR regulon has been increasingly characterized in prototypical strains such as PA14 and PAO1, the broader relevance of PqsE across diverse strains remains insufficiently explored. In this study, *pqsE* and *rhIR* were found to be genetically conserved among twelve phylogenetically diverse *P. aeruginosa* strains. Phenotypic assays and metabolite profiling demonstrated that PqsE broadly influences key virulence traits and multicellular behaviors, including pyocyanin production and biofilm formation. Importantly, PqsE was found to be essential for HAQ biosynthesis in most strains, challenging earlier assumptions based on prototypical strains.

Although the extent of these PqsE-dependent phenotypes varied among strains, core functions were consistently preserved, indicating both evolutionary conservation and strain-specific modulation. These findings deepen our understanding of QS regulation and reinforce the central role of PqsE across *P. aeruginosa* populations.

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Chatting at the Extremes: How Quorum Sensing Changes Across Extreme Environments

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Quorum sensing (QS) is a sophisticated cell-to-cell communication mechanism used by microorganisms to sense their environment and coordinate collective behaviors. This system relies on the production, release, and detection of specific extracellular signal molecules, which accumulate according to population density. Once a critical threshold concentration is reached, these signals trigger coordinated gene expression across the microbial population. In natural context, QS is widespread and can affect a broad range of biological processes, including nutrient cycling, biofilm formation, host-microbe interactions, and environmental adaptation. Several QS systems have been identified, each relying on specific signal molecules and pathways. This diversity carries important implications, as certain signaling molecules exhibit greater stability than others under specific environmental conditions.

In extreme environments, where harsh conditions push life to the edge of its survival limits, microbes are often the only form of life capable of surviving and thriving. Although still poorly understood, it is possible that QS plays a crucial role in regulating their adaptive responses to environmental stressors.

This study aims to describe patterns in the distribution of QS genes in diverse extreme environments. We annotated a QS-related proteins database with KEGG Orthology (KO) identifiers and compared them to KO profiles from our metagenomic dataset, comprising samples from over 300 extreme sites worldwide; these latter were also characterised through high resolution geochemical analyses. Overall, this comparison allowed us to evaluate the presence, distribution, and relative abundance of QS-related functions across different environmental and geochemical contexts.

"Cell-cell communication in bacteria: new insights and future trends"

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Identification of culturable bacteria associated with the rhizosphere of *Lablab purpureus* growing in Namibia.

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Dolichos lablab (*Lablab purpureus* (L.) Sweet)) is a multipurpose drought tolerant protein-rich legume crop native to Africa and grown in warm temperate to tropical climates for its edible seeds and manure. *Lablab purpureus* holds significant benefits to subsistence farmers and offers a great promise for sustainable crop productivity, especially in marginalised areas. Its uses range from human consumption as a vegetable to improving soil fertility, and as forage. Notwithstanding *Lablab purpureus* crucial potential functions in Namibia, there is currently limited information regarding the plant's rhizosphere bacteria. The study aimed at identifying *Lablab purpureus*' natural rhizosphere bacteria. Isolation of rhizosphere bacteria involved the use of general media (Luria Bertani agar and tryptic soy agar); selective media such as *Rhizobium* and Yeast Extract Mannitol (YEM) Congo red from soil sample extracts. Eighty-five strains of bacteria were isolated and were subsequently identified by 16S rRNA gene sequencing analysis. The results showed that they belonged to the following genera, *Bacillus*, *Streptomyces*, *Exiguobacterium*, *Stutzerimonas*, *Rhizobium*, *Acidovorax*, *Agrobacterium*, *Psychrobacter*, *Priestia*, *Planococcus*, *Bhargavaea*, *Stenotrophomonas*, *Caulobacter*, *Peribacillus*, *Niallia*, *Athrobacter*, *Sphingobium*, *Enterobacter*, *Sphingobacterium*, *Sinorhizobium*, *Flavobacterium*, *Microbacterium*, *Metabacillus*, *Neobacillus*, and *Pseudomonas* which are reported to have growth promoting substances. The study highlighted the potential use of these plant growth promoting rhizobacteria for inocula production or biofertilisers for enhancing growth and nutrient content of beans and other crops under field conditions. The study was the first report of *Lablab purpureus*'s rhizosphere associated bacteria in Namibia.

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Modulation of signal transduction in *Pseudomonas aeruginosa* by metabolites from *S. didymobotrya* leaves

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Introduction

Bacteria communicate and coordinate their group behavior through a process known as quorum sensing (QS). This system relies on the release and detection of small signaling molecules (autoinducers), which, upon accumulating to a specific concentration, activate internal cellular pathways which lead to synchronized gene expression and trigger the production of 'social goods', such as virulence factors, toxins, biofilms, across the bacterial population. This cooperative behavior allows bacteria to adapt and thrive in challenging environments.

Aim

As since nature is rife with natural QS inhibitors, a promising approach to combat bacterial pathogenicity involves disrupting QS, essentially identifying compounds that interfere with bacterial communication without killing the bacterial cells. Although the popular medicinal plant *S. didymobotrya* has been studied extensively, surprisingly little is known about its effect on bacterial QS. In this study, we decided to examine whether *S. didymobotrya* has the ability to modulate QS in *P. aeruginosa*.

We extracted plant metabolites with organic solvents, performed untargeted metabolomics analyses and identified several putative metabolites as potential QS modulators. We tested the effects of these metabolites on several virulence factors, such as pyocyanin production, biofilm formation and motility, on overnight cultures of *Pseudomonas aeruginosa*. One of these compounds showed promising anti-virulence properties.

Key words

autoinducers, biofilm, harmaline, pyocyanin, virulence factors, quorum sensing.

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Macrocycles as an Anti-Virulence Strategy Against Resistant Gram-Negative Pathogens

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The limited diversity of available antibiotic targets has placed a large strain on the treatment of bacterial infections, as resistance mechanisms that undermine their efficacy are becoming increasingly widespread. To address this challenge, we employ anti-virulence strategies based on host–guest interacting macrocycles. Unlike conventional antibiotics, these molecules are non-bactericidal and non-bacteriostatic; instead, their mechanism of action involves binding to homoserine lactones (HSLs) and lipopolysaccharides (LPSs)—two critical virulence factors in Gram-negative pathogens.

Our macrocycles demonstrate potent activity against Top Priority carbapenem- and third/ fourth-generation cephalosporin-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. They suppress toxin production and promote biofilm eradication while simultaneously enhancing the penetration and effectiveness of standard-of-care antibiotics when used in combination therapies.

In eukaryotic cells, the sequestration of HSLs and LPSs diminishes their direct toxic effects on cellular membranes, thereby neutralizing critical mechanisms that promote bacterial colonization and weaken host immune defenses—observed in both in vitro and in vivo models. Since both targets are extracellular bacterial factors, this approach effectively circumvents conventional antibiotic resistance pathways and minimizes the risk of rapid tolerance or resistance development.

The versatility of macrocyclic host–guest chemistry provides a powerful platform for designing tailored anti-virulence therapies across a broad spectrum of Gram-negative infections, offering a complementary path to overcoming the global antibiotic resistance crisis.

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N-acyl homoserine lactone quorum sensing in root associated *Enterobacter asburiae* AG129

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Proteobacteria commonly use a contact independent cell-cell communication system known as quorum sensing (QS) mediated by N-acyl-homoserine lactone (AHLs) signal molecules. The canonical AHL QS system involves a luxI-family gene which encodes an AHL synthase, and a luxR-family gene, which encodes a transcriptional regulator responsive to the cognate AHLs. This study involves the AHL QS system of *Enterobacter asburiae* AG129, a root associated endophyte strain isolated from rice (*Oryza sativa*). *E. asburiae* AG129 produces the N-butanoyl homoserine lactone (C4-AHL) signal molecule. Genome sequencing of strain AG129 and annotation revealed the presence of a canonical AHL QS system, comprising genetically adjacent *easI* and *easR* genes. A genomic *easI* knockout mutant was created that could no longer produce AHLs and in trans complementation with a plasmid carrying the *easI* gene restored the AHL production in the *easI* mutant. AHL QS regulation in AG129 was shown to influence root colonization and secretome analysis revealed a significant role in the regulation of Type VI secretion system (T6SS) cluster proteins. GC/MS analysis identified sixteen volatile compounds (VOCs) which are more abundantly emitted by the wild type compared to the *easI* knockout mutant. These findings suggest that AHL QS in *E. asburiae* AG129 positively regulates T6SS and several VOCs production while negatively impacts the rice root colonization. This is a first study on the role of QS signaling in a bacterial endophyte.

Keywords: *Enterobacter asburiae* AG129, endosphere/rhizosphere, N-butanoyl homoserine lactone (C4-AHL), quorum sensing, Type VI secretion system (T6SS), Volatile organic compounds (VOCs)

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Functional characterization of highly expressed small RNAs in *Pseudomonas aeruginosa* within the polymicrobial environment of cystic fibrosis

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Cystic fibrosis (CF) is commonly associated with polymicrobial infections, with *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida albicans* being among the most frequent species isolated from sputum samples. To adapt and survive in this complex and competitive environment, *P. aeruginosa* must precisely tune its gene expression and small RNAs (sRNAs) represent a fine way to shape its physiology upon exposure to stress conditions. Through RNA-seq analysis of samples from an in vitro continuous-flow system that recapitulates CF-associated polymicrobial infections with high fidelity and stability, I analysed highly expressed intergenic regions. This led to the identification of several sRNA candidates that may contribute to the regulation of *P. aeruginosa* physiology in the CF context. Among them, a conserved sRNA in *Pseudomonas* spp, previously identified in other studies but not functionally characterized, was found to positively influence OprE porin abundance. OprE, one of the most numerous porins, primarily serves as an entry point for carboxylate-containing nutrients and may confer a competitive advantage when overexpressed. Another sRNA is transcribed from the intergenic region flanking the *aceA* gene which is essential for acetate utilization. This sRNA is predicted to originate from the 5' untranslated region of the *aceA* gene, as they share the same transcription start site. Initial findings indicate that overexpression of the sRNA prevents growth on acetate as the sole carbon source. This preliminary data indicates a possible role in acetate metabolism regulation, crucial for *P. aeruginosa* as it utilizes acetate, abundant in airways secretions and acetoin, a by-product of *S. aureus* metabolism which has been shown to represent a cooperative interaction between the two species. Taken together, these results suggest multiple RNA-mediated mechanisms through which *P. aeruginosa* modulates its metabolism in CF-related polymicrobial infections.

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Synthesis and Evaluation of Pyrazinone Photoaffinity Probes for Interspecies Quorum Sensing Receptor Identification

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Most bacterial species communicate with each other and other microorganisms through a process known as quorum sensing (QS), which involves the production, release, and detection of extracellular signaling molecules called autoinducers (AIs). One class of QS signal molecules, of which autoinducer-3 (AI-3) and DPO are the best-known examples, contains a pyrazinone scaffold that generally results from the condensation of two amino acids. These signaling molecules have been identified in *Vibrio cholerae* and in other clinically relevant pathogens, where they regulate virulence-associated phenotypes and influence host immune responses, thereby playing a crucial role in interspecies signaling. However, the specific receptors for most of these signals and the molecular mechanisms underlying pyrazinone-mediated QS remain poorly understood.

This research aims to address this knowledge gap by synthesizing and evaluating AI-3/DPO analogs to study their interactions with QS receptors in several bacterial species, including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Enterococcus faecalis*; by utilizing a method termed 'activity-based protein profiling' (ABPP), we aim to identify proteins that bind to AI-3, thereby potentially uncovering new insights into the mechanism of action of AI-3 and its analogs. This work is expected to provide novel insights into bacterial communication mechanisms and could facilitate the development of antimicrobial strategies targeting QS pathways.

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Decoding the Regulatory Role of the LuxR solos PsaR3 in *Pseudomonas syringae* pv. *actinidiae* virulence

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The highly virulent biovar 3 of *Pseudomonas syringae* pv. *actinidiae* (Psa), the eziological agent of the kiwifruit bacterial canker, harbors a plasmid-encoded LuxR solo, namely PsaR3. Unlike canonical LuxR proteins, PsaR3 lacks a known cognate AHL synthase, and its activation mechanism(s) and targets remain unclear.

A transcriptomic analysis performed with a strain overexpressing an inducible PsaR3 revealed the upregulation of genes related to virulence, including the type III secretion system (T3SS) and motility, as well as the plasmid-borne cluster containing *psaR3*. Within this cluster, an intergenic region (IR) located between the two opposite operons was found to act as a bidirectional promoter, regulated by PsaR3, though in absence of any exogenous inducer signal. This suggested that (i) the signal may be endogenously produced by Psa, or (ii) the overexpression of PsaR3 may lead to its spontaneous autoactivation.

To allow a «controlled» post-translational activation of PsaR3, we designed and constitutively expressed a chimeric protein including the DNA-binding domain of PsaR3 and the AHL-responsive autoinducer-binding domain of the well-characterized CviR from *Chromobacterium violaceum*. Interestingly, though displaying a phenotype different from the control, the strain expressing the chimera did not respond to AHLs, thus supporting the hypothesis of an autoactivation. Moreover, the CviR-expressing strain showed an impaired T3SS activation, suggesting that the constitutive activation may generate a negative feedback, likely to avoid a persistent virulence induction, or that the structure of the chimeric sensor led to a loss-of-function protein acting as a dominant negative mutant. We are currently investing the phenotype of a strain overexpressing constitutively the native form of PsaR3 to get insights into its mechanism of induction and its function.

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Antibacterial anti-virulence properties of natural products in honey, and their effects on *Acinetobacter nosocomialis*

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Bacteria communicate through quorum-sensing (QS) mechanisms that involve the production and detection of signaling molecules called autoinducers. As bacterial cell density increases, autoinducer concentrations rise and, upon reaching a threshold, trigger coordinated gene expression changes. These changes can lead to increased virulence, biofilm formation, and antibiotic resistance.

Honey, known for its therapeutic properties, contains various natural products with antibacterial effects. Our research focuses on identifying compounds in honey, specifically phenolic acids, flavonoids, and indoles, that may lower bacterial virulence and antibiotic resistance.

This study focuses on *Acinetobacter nosocomialis*, a Gram-negative bacterium associated with nosocomial infections, and this pathogen is known for its multidrug resistance and twitching motility that contribute to biofilm development. We investigate the impact of organic honey extracts on a set of virulence factors of *A. nosocomialis*, aiming to explore their potential health-promoting role.

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PHB/TiO₂/GO films bind n-acyl homoserine lactones to control bacterial quorum sensing in *Pseudomonas aeruginosa*

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Quorum sensing is a key mechanism in virulence and pathogenesis of Gram-negative bacteria. Hence, inhibition of quorum sensing could be a suitable alternative strategy of antimicrobial therapy. Autoinducers of quorum sensing such as N-acyl homoserine lactones (AHLs) are essential in chemical signaling, biofilm formation and pathogenesis. In this study, the potential for biosensor development was evaluated by analyzing polyhydroxybutyrate (PHB) films functionalized with titanium dioxide (TiO₂) nanoparticles and graphene oxide (GO), as sensitive and environmentally friendly biosensing materials. The study focused on the interactions between PHB/ TiO₂/GO films and three AHL molecules namely, N-hexanoyl-homoserine lactone (C6-HSL), N-octanoyl-homoserine lactone (C8-HSL), and N-decanoyl-homoserine lactone (C10-HSL). The results revealed that there was stable binding of AHLs onto the PHB/ TiO₂/GO surface, with root mean square deviations (RMSD) of <2.5 Å. As such, the findings point to the potential structural stability of the films for binding the autoinducers. Moreover, our findings show binding free energy values ranging from -25 to -40 kJ/mol, which are indicative of strong interactions. The binding stability of PHB/ TiO₂/GO films is attributed chemical interactions such as hydrogen bonding and van der Waals forces as well as the π - π stacking property of graphene oxide. This study demonstrates the feasibility of the modelled PHB/ TiO₂/GO films as sustainable and efficient materials for use as bacterial biosensors to mitigate against quorum sensing in pathogenic gram-negative bacteria.

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Outer membrane vesicles (OMVs) secreted by *Paraburkholderia phytofirmans* PsJN: characterization of associated RNA content and interaction with plant cells

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Plant growth-promoting bacteria (PGPB) support plant development, increase productivity, and improve resilience to stress. These benefits arise from complex interactions between species, involving the exchange of various signaling and effector molecules. Extracellular vesicles (EVs) are an important means of signaling between cells, organisms, and even across biological kingdoms. Among EVs, outer membrane vesicles (OMVs)—produced by Gram-negative bacteria—can elicit both immune-activating and immune-suppressing responses in plants. However, direct interaction between OMVs and plant cell membranes has been shown for only a single phytopathogenic bacterial strain. Even less is known about the role of OMVs in symbiotic relationships between plants and beneficial bacteria, with existing data mostly limited to rhizobia-legume systems.

To explore OMV-mediated interactions between non-rhizobial plant-beneficial bacteria and plant cells, we isolated and characterized OMVs from *Paraburkholderia phytofirmans* PsJN—a well-known plant growth-promoting and stress-mitigating strain effective across various plant species. Using OMVs labeled with the fluorescent lipid-binding dye Vybrant™ DiD and visualization via confocal laser scanning microscopy, we demonstrated that PsJN-OMVs directly interact with the root hairs and epidermal cells of *Arabidopsis thaliana* and tomato. Using the membrane fusion probe octadecyl-rhodamine B chloride (R18), we confirmed that PsJN-OMVs can fuse with plant cell membranes. We examined the RNA content of PsJN-OMVs. The OMV-associated RNA, which was mostly sized up to 200 nt, was sequenced using the DNBSEQ Sequencing Platform. Prior to library synthesis, samples were separated into two subsamples: one up to 40 nt and the other from 40 to 200 nt. These were then sequenced using the SE50 and PE100 approaches, respectively. The same procedure was used for small RNA isolated from PsJN cells. Comparison of RNA sequences from PsJN OMVs and cells showed substantial differences in their size distribution, biotypes, and genome regions of origin. The results indicate that the packaging of RNA into PsJN-OMVs is not random, but involves the selective enrichment of certain RNA species in OMVs, while others are predominantly retained within the cells. Previous studies suggested that EVs may both remove unnecessary cellular RNAs and transfer RNAs to other cells, as signaling functions. The molecular mechanisms for selective loading of eukaryotic EVs are only partially described, while those responsible for bacterial vesicles are poorly understood. The data on RNA associated with OMVs secreted by plant beneficial bacteria are even more scarce. Our results make a significant step toward understanding the role of OMVs in the initial phases of root colonization and symbiosis establishment. Advancing knowledge in this field may lead to the development of innovative, environmentally friendly strategies to address agricultural challenges and promote sustainable crop production.

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Delayed Competitive Signaling and Virulence Modulation by a Rhizospheric Bacterium

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Microbial communities coordinate behaviors through complex chemical signaling networks that govern growth, virulence, and ecological fitness. Understanding these interspecies interactions is essential to reveal unique signaling modalities and to develop potent anti-virulence strategies against bacterial pathogens, that may circumvent resistance development. We surmise that such natural strategies already exist in soil ecosystems. We isolated a rhizospheric bacterium, GH8, coexisting with *Bacillus subtilis*, which produces diffusible metabolites that modulate microbial physiology in a context-dependent manner. The cell-free supernatant of GH8 exhibits potent inhibitory activity against *B. subtilis* (MIC 0.625 mg/mL) and selectively attenuates virulence-associated phenotypes in *Pseudomonas aeruginosa* strains PAO1 and PA14, reducing pyocyanin production (> 40%) and biofilm formation (> 65%) at sub-inhibitory concentrations, without impairing planktonic growth. Temporal co-culture assays on agar medium reveal that GH8 exerts antagonism against *B. subtilis* only when pre-established, suggesting production of time-regulated diffusible signals involved in competitive and defensive interactions. These findings imply a sophisticated regulatory mechanism of interspecies communication. The CFS are undergoing characterization for metabolomic profiling. Concurrent whole genome sequencing of GH8 aims to uncover biosynthetic gene clusters and regulatory networks underlying these interactions. Our work reveals a model of delayed competitive signaling in soil bacteria, highlighting the complexity of chemical communication shaping microbial community dynamics.

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Optimising Plant Symbiotic Bacteria Through Quorum-Sensing and Engineering Biology for Sustainable Nitrogen Fertilisation

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The excessive use of chemical nitrogen fertilisers has significantly contributed to environmental challenges such as water pollution and greenhouse gas emissions. As a sustainable alternative, plant-symbiotic diazotrophic bacteria like *Gluconacetobacter diazotrophicus* (Gd) can promote plant growth and naturally fix atmospheric nitrogen. Gd possesses a LuxI/LuxR-type quorum sensing (QS) system, which uses N-acyl homoserine lactones (AHLs) to regulate gene expressions in response to cell density. This study investigates QS in Gd to assess its regulatory influence on genes associated with plant growth promotion, nitrogen fixation, and seedling colonisation, with the broader objective of enhancing the biofertiliser potential of Gd through molecular genetic manipulation. Genome analysis and PCR-based screening of ten globally sourced Gd strains revealed the presence of luxI/luxR homologs in three strains, indicating a limited and strain-specific distribution of QS circuitry. LC-MS/MS profiling identified eight distinct AHLs, several of which possessed a hydroxyl group at the third carbon (3-OH AHLs). Notably, the detection of 3-OH AHLs contrasts with previously reported 3-oxo AHLs in the Gd PAI5 strain. Among the identified signals, 3-OH-C10-AHL was the predominant molecule. To investigate the functional relevance of QS, targeted mutagenesis was employed in strain K4 (PAI5). The luxI homolog (AHL synthase gene) was disrupted via in-frame deletion, confirmed by loss of AHL production in LC-MS/MS analysis. AHL synthesis was restored upon genetic complementation, demonstrating functional knockout and knock-in. To elucidate the regulatory scope of QS, transcriptomic analysis via RNA-seq is underway comparing wildtype, knockout, and complemented strains. This will identify QS-regulated genes potentially involved in nitrogen fixation, plant colonisation, and other plant-growth-promoting activities. Our findings provide new insights into the QS network in Gd and its role in regulating agriculturally relevant functions. Understanding and manipulating QS could enable the development of biofertiliser strains with enhanced efficacy, contributing to more sustainable agricultural practices.

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The putative AHL receptor SdiA as a Repressor of Phagocytosis and Intracellular Survival in *Klebsiella pneumoniae*: Insights from Macrophage and Amoeba Models

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Klebsiella pneumoniae is a significant opportunistic pathogen, and the rise of multidrug-resistant strains necessitates new therapeutic strategies targeting virulence. In *Escherichia coli*, the quorum-sensing receptor SdiA has been implicated in regulating key infection processes such as adhesion to biotic surfaces and acid resistance. This study aimed to elucidate the role of SdiA in the pathogenesis of *K. pneumoniae*, focusing on its impact on adhesion, phagocytosis and intracellular survival.

We utilized two *K. pneumoniae* strains, the multi-drug resistant clinical isolate KLEB-33 and the type strain ATCC 13883T. An isogenic *sdiA* deletion mutant ($\Delta sdiA$) was generated for each strain using a CRISPR-Cas9 system². The role of SdiA in virulence was assessed using an amoeba predation model to evaluate resistance to phagocytosis, and an in vitro infection model with immortalised murine bone marrow-derived macrophages (iBMDMs) to study adhesion, phagocytosis, and intracellular survival dynamics. Capsular polysaccharide production was estimated by uronic acid quantification.

Deletion of *sdiA* resulted in a significant decrease in uronic acid content, suggesting that SdiA positively regulates capsule production, as suggested by previous results on serum sensitivity². This correlated with increased susceptibility to phagocytosis, as $\Delta sdiA$ strains formed larger trophozoite halos in the amoeba predation assay, and showed 1.5 to 2.5-fold higher adhesion and uptake by iBMDMs compared to wild-type strains. Paradoxically, despite being more readily phagocytosed, the $\Delta sdiA$ mutants exhibited enhanced intracellular survival within macrophages. This suggests that while SdiA promotes capsule-mediated protection against initial phagocytic uptake, it may repress an alternative mechanism crucial for survival once inside the host cell. The study highlights a dual and complex role for SdiA in modulating the interaction between *K. pneumoniae* and phagocytic cells.

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A LuxR solo widespread among *Pseudomonas* spp

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LuxR solo (orphan) regulators, which lack paired LuxI synthases, mediate non-canonical quorum sensing (QS) in plant-associated bacteria. Here, we characterize a novel LuxR solo system in *Pseudomonas brassicaceum*, co-located with anthranilate synthase genes (*trpE/trpG* homologs) in a conserved operon structure found in over 170 plant-associated *Pseudomonas* species. We generated four targeted mutants: an in-frame deletion of *luxR*, two anthranilate synthase mutants (in-frame and kanamycin-disrupted), and a deletion of a divergent neighboring operon. Promoter activity, assessed using a promoter probe plasmid vector via gene promoter-lacZ transcriptional fusion, showed more than 50% reduction in the in-frame anthranilate mutant, suggesting an involvement of anthranilate-derived signals in the studied LuxR system. Phenotypic assays revealed that phosphate solubilization was inactive in the wild type but induced in the LuxR and anthranilate mutants. Auxin was produced only in the LuxR mutant, while protease activity was lost across all three mutants. Motility was abolished exclusively in the LuxR mutant. This study reveals a previously unrecognized anthranilate-responsive LuxR solo system regulating key plant-interactive traits in *P. brassicaceum*, with implications for QS with a novel signal in plant-associated *Pseudomonas*.

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Impact of a quorum sensing molecule (3-oxoC12:2) on intestinal barrier function during inflammation using gut-on-chip technologies

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Introduction: In inflammatory bowel disease (IBD), the intestinal barrier is disrupted, leading to epithelial damage, excessive immune activation, and microbiota alterations. We previously identified that 3-oxo-C12:2-HSL, a quorum sensing molecule of the N-acyl-homoserine lactone family, is abundant in healthy individuals but reduced in IBD patients. Earlier studies showed its protective action on epithelial tight junctions and immunoregulatory effects under inflammation. To further explore these properties, we established an intestinal inflammation-on-chip model to evaluate its impact on barrier function and immune cell recruitment.

Materials and Methods: The organ-on-chip (OOC) system reproduces the intestinal epithelial interface under dynamic flow, mechanical stress, and 3D organization. Intestinal epithelial cells (Caco-2/TC7) were cultured in the upper channel, while endothelial cells (HUVEC) and immune cells (PBMCs or neutrophils) were introduced in the lower channel. Inflammation was induced with pro-inflammatory cytokines or lipopolysaccharides (LPS), and 3-oxo-C12:2-HSL was added to the epithelial compartment. Barrier integrity, cytokine secretion, and immune cell recruitment were assessed.

Results: With PBMCs, 3-oxo-C12:2-HSL reduced LPS-induced hyperpermeability by $49.5 \pm 8\%$ and cytokine-induced hyperpermeability by $14.2 \pm 2.8\%$. It also decreased MCP-1 secretion by $26 \pm 8\%$ in response to LPS, as well as IL-6 and IL-8 levels under cytokine stimulation. Similar effects were observed with neutrophils: hyperpermeability decreased by $50.5 \pm 7.8\%$ and IL-6 secretion by $37 \pm 21\%$. Importantly, immune cell recruitment was also limited: PBMC infiltration into the epithelial compartment decreased by $56.2 \pm 15.5\%$ and neutrophil recruitment by $40.6 \pm 9.2\%$ (Fig.1).

To improve physiological relevance, colon organoids were substituted for epithelial cell lines. Preliminary data suggest that 3-oxo-C12:2-HSL similarly prevents inflammation-induced barrier disruption and reduces cytokine secretion in this model.

Conclusion:

Our inflammation-on-chip model shows that 3-oxo-C12:2-HSL preserves intestinal barrier integrity by reducing permeability, cytokine release, and immune cell infiltration, supporting its potential role in intestinal homeostasis.

"Cell-cell communication in bacteria: new insights and future trends"

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Antivirulence Potential of 4-Aminoquinoline-Adamantane Derivatives Against Gram-Negative Pathogens

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Biofilms play a central role in the persistence and pathogenesis of bacterial infections as they form a protective niche that shields the bacteria from host immune responses and antibiotic therapy. These surface-attached communities contribute significantly to chronic and device-associated infections. In Gram-negative pathogens, biofilm formation and virulence are regulated by quorum sensing (QS) — a cell density-dependent system that coordinates gene expression. Targeting QS, rather than bacterial viability, represents a promising antivirulence strategy that may reduce selective pressure for resistance and preserve commensal microbiota. In our previous study, long-chain 4-aminoquinoline derivatives showed a strong QS inhibitory effect in *Pseudomonas aeruginosa*. Based on this, we synthesised six novel hybrids of 4-aminoquinoline and adamantane (KBK07, KBK56, KBK63, KBK64, KBK66 and KBK80) to investigate how variations in the substitution of the terminal amino group affect the biological activity. Their ability to interfere with QS pathways was investigated using *P. aeruginosa* and *Chromobacterium violaceum* CV026 biosensor strains, at concentrations that do not interfere with bacterial growth. Inhibition of biofilm formation was evaluated in *P. aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli* and *Klebsiella pneumoniae*. Toxicity and in vivo efficacy were investigated using a zebrafish infection model.

KBK80 showed the strongest and broadest activity, inhibiting the PQS and Rhl systems by 70 % and 75 % respectively, with a moderate effect on Las (20 %). It reduced *P. aeruginosa* biofilm by ~40% and suppressed pyocyanin production by 26%. KBK80 also inhibited biofilm formation in *A. baumannii*, *E. coli* and *K. pneumoniae* by 28%, 22% and 48%, respectively. KBK07 inhibited biofilm formation in all four strains by up to ~40%, while KBK64 with minimal QS inhibition in *P. aeruginosa* strongly suppressed violacein production and inhibited biofilm formation in *A. baumannii* by 65%.

These results show that 4-aminoquinoline- adamantane derivatives can be developed into promising broad-spectrum antivirulence agents.

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Azotobactin siderophore as a potential intermediary of the beneficial effect of co-culture with *Bacillus subtilis* 3610 and *A. vinelandii* on enhanced nitrogen fixation

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Soil bacteria play a fundamental role in nutrient cycling and in the availability of specific elements, such as nitrogen (N), but the impact of intercellular interactions on these activities is seldom examined. Recently, we observed that co-cultivating the diazotrophic bacterium *A. vinelandii* with the plant-promoting bacterium *Bacillus subtilis* enhanced nitrogen fixation by the former under nitrogen-deficient conditions (Leroux et al., 2024). *B. subtilis* used this additional bioavailable N for its metabolism and growth. However, the mechanisms underlying the increased N fixation and transfer to *B. subtilis* remain unknown. We hypothesised that part of the transfer process may be mediated by siderophores, Fe³⁺-chelating molecules that facilitate uptake from the environment, as these molecules are rich in N. Indeed, when *A. vinelandii* was cultivated in an N-free medium supplemented with Fe-citrate, we observed a reduction in the secretion of the siderophore azotobactin that correlated with a decrease in the growth of *B. subtilis*. To further explore whether *Bacillus* species could utilise azotobactin as a nitrogen source, we performed a purification and then added it to an N-free medium in which different *Bacillus* species were inoculated. We observed that azotobactin supplementation decreased sporulation in *B. subtilis* 3610 and *B. velezensis* PTB102, but not in *B. halotolerans* PTB108, suggesting a strain-specific effect. Additionally, comparative genomics analysis of strains promoting N-fixation versus those that did not revealed no differences in sporulation-related genes. Deletion mutants of these genes will be used to determine if the *Bacillus* sporulation pathway plays a role in mediating the positive effects on N-fixation by *A. vinelandii*. In summary, we unveiled a complex interaction between a diazotroph and a plant growth-promoting bacterium. This observation highlights that the influence of bacteria on nutrient bioavailability in soil should be viewed through the lens of community activity rather than focusing solely on individual organisms.

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Modulation of Autoinducer-2 Levels in the Mouse Gut: Chemical Strategies for Deciphering Bacterial Communication Mechanisms

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Autoinducer-2 (AI-2) stands out from other quorum sensing signals due to its ubiquity across bacterial species, and its unique ability of fostering cell-cell signalling between bacteria from different phyla in complex multispecies communities. AI-2 does not refer to one molecule, but instead various cyclic forms in equilibrium of their precursor (S)-4,5-dihydroxy-2,3-pentanedione (DPD), with different forms being recognised by distinct receptors.[1] The dynamic chemical character of this signal has convoluted the study of its roles in bacterial communication since its discovery. Our group focuses on the chemical synthesis and application of useful tools for studying the mechanisms related to AI-2 communication and manipulating AI-2 levels in vivo.[2] We have recently described a powerful analytical GC-MS procedure that enabled accurate quantification of AI-2 in mice intestinal samples, allowing us to measure the effect of different in vivo AI-2 manipulation strategies.[3] One of these strategies is the use of β -glycosylated DPD prodrugs, which bypasses the problem of AI-2 chemical and metabolic instability and allows for administration and targeted release of AI-2 in the intestine, where the β -glycosyl bond can be broken down by gut microbiota enzymes, slowly increasing AI-2 levels without the need for inoculation with different bacteria species. We believe that these prodrugs can even be of therapeutic value to help mitigate adverse effects of antibiotic-induced microbiota imbalances. Overall, our innovative chemical-based strategies for the study of AI-2 communication contributes to clarify bacterial communication mechanisms and ultimately translate into potential therapeutic benefits to the gut microbiota and its host health.

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Regulatory effects on biofilm formation revealed by *sdiA* mutation in *Klebsiella pneumoniae*

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The formation of biofilms is a significant virulence factor in *Klebsiella pneumoniae*, a bacterium recently classified by the WHO as a maximum-priority pathogen for developing new antimicrobial strategies due to its multi-resistance (MDR) and hypervirulence traits. SdiA, a quorum-sensing receptor that responds to acyl-homoserine lactones (AHLs), plays an important regulatory role in biofilm formation in Gram-negative bacteria. However, the role of this receptor in *K. pneumoniae* remains unclear. The present study utilised the Rolling Biofilm Bioreactor system to investigate the impact of AHL signalling in both wild-type and *sdiA* deficient ($\Delta sdiA$) strains of *K. pneumoniae* KLEB-33, an MDR hyper-biofilm-forming strain harbouring hypervirulence genes. Quantification of biofilm biomass was conducted at 24-hour intervals (up to 72 hours) using a Crystal Violet staining method and Confocal microscopy examination. Furthermore, biofilms were examined for cell filamentation and matrix composition after eDNA and exopolysaccharide fluorescent dye staining. The results obtained demonstrated that, in comparison with the parental strain, the $\Delta sdiA$ mutant exhibited enhanced biofilm formation and elevated rates of cell filamentation. Additionally, it was observed that AHL supplementation promoted biofilm formation exclusively in the wild-type strain, with no such effect observed in the $\Delta sdiA$ mutant. This finding suggests that AHL biofilm promotion is SdiA-dependent. Furthermore, no significant alterations in matrix composition were detected after *sdiA* mutation or AHL supplementation. Consistent with observations made in other bacteria, our results indicate that SdiA is a biofilm-repression regulator in *K. pneumoniae*, and its biofilm-repression effect could be related to cell filamentation in sessile communities of this pathogen.

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Changes in Bilirubin Metabolism Correlate with Inflammatory Bowel Diseases and Gut Microbiota

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Molecular links between gut microbiota dynamics and host health in Inflammatory Bowel Diseases (IBD), particularly those involving the bilirubin metabolic pathway, are critical for understanding disease pathophysiology. Imbalances in the gut microbiome are known to affect IBD. Since bilirubin and its derivatives have antioxidant properties, microbial disruption of their metabolism could exacerbate intestinal inflammation. A multi-omics approach was used, analyzing fecal samples from 119 IBD patients (Crohn's disease and ulcerative colitis) and healthy controls via a combination of untargeted and targeted UPLC/HRMS-based metabolomics and shotgun metagenomic sequencing. Our results revealed significantly lower levels of specific bilirubin metabolites in IBD patients, alongside reduced gut bacterial diversity in active disease. A strong positive correlation was identified between the abundance of Lachnospiraceae bacteria and key bilirubin metabolites. These findings suggest that disruption of the bilirubin catabolic pathway is a key feature in IBD pathophysiology, highlighting a novel metabolic role for Lachnospiraceae and potentially identifying new biomarkers for disease activity.

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Characterization of AHL-QS based system in *P. gessardii* isolated from raw milk and its role in spoilage activity

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Quorum-sensing is a bacterial signaling pathway and involved in the regulation of genes expression. Yet, its role in food spoilage is not well explored. *Pseudomonas* are a main spoilage species in dairy products. During storage of raw milk under cold conditions before thermal processing (pasteurization and ultra heat treatment), there will be production of spoilage thermostable protease enzymes by *Pseudomonas* spp. Furthermore, regulation of other spoilage factors such as biofilm formation and motility by QS is still under-researched. In this project, *Pseudomonas* with high spoilage activity at 4°C and 25°C were isolated from raw milk and identified at species level. After that, they were subjected for downstream analysis. First, investigation and characterization of acyl homoserine lactones-QS system in the test isolates by analysis of the whole genomic sequences, application of biosensor assays for detection of AHL production, and liquid chromatography-mass spectrometry analysis. Second, constructions of LuxI mutants to investigate the effect of AHL on the phenotypic characteristics, comparing with the wild-type of the strains. Third, testing QS inhibitors identified by molecular docking analysis on the effect of spoilage phenotypes, in particular, proteolytic activity in milk. The latter results will be compared with objective 2 to obtain better understanding about the reliability of in silico approaches to investigate the association of QS with phenotypic characteristics. Six different strains that showed high spoilage activity were isolated from raw milk and found belong to *P. gessardii*. They all have LuxRI-QS based system producing short chain AHL, mainly C4-HSL. In this presentation, the results about phenotypes and LuxRI-QS characterization in *P. gessardii* will be presented, in addition to the results of ongoing activities regarding the effect of AHL-QS system on spoilage phenotypes in *P. gessardii*. This will provide future insights for food industry to control spoilage activity by application of QS inhibitors.

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Interactions between the *Pseudomonas aeruginosa* Las quorum-sensing system and stringent response reveal distinct mechanisms of resistance to ceftazidime and piperacillin

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In *Pseudomonas aeruginosa*, the acyl-homoserine lactone (AHL)-dependent Las quorum-sensing system enhances resistance to multiple antibiotics, including the clinically important β -lactam ceftazidime. β -lactams susceptibility is also influenced by the stress-inducible stringent response system, which increases detoxification of reactive oxygen species (ROS) in non-growing cells to maintain membrane integrity and mitigate antibiotic internalization. Here, we examine the interaction of LasR with stringent response (SR) in shaping resistance to the β -lactam antibiotics ceftazidime and piperacillin. Our results showed that disrupting LasR decreases resistance to ceftazidime but not piperacillin. LasR also increases ROS levels and uptake of ethidium bromide, a proxy for measuring membrane permeability, similar to that of the SR system. We could restore ceftazidime resistance and membrane resistance in the Δ lasR mutant by chemically or enzymatically detoxifying ROS. These results suggest LasR increases ceftazidime resistance through a shared pathway of ROS detoxification and protecting membrane integrity. In support of this idea, concurrently disrupting both the LasR and SR systems resulted in a non-additive effect on ceftazidime resistance that was similar to that of disrupting the individual systems. In contrast, we observed a different pattern for piperacillin. Individually disrupting LasR or SR had little to no effect on resistance, while disrupting both systems caused >10-fold decrease in resistance, revealing synergistic effects of these two systems that did not correspond to membrane permeability changes. These results indicate LasR and SR confer piperacillin resistance through synergistic but different mechanisms potentially unrelated to membrane permeability. Together, our work reveals new mechanistic insights into how LasR and stringent response contribute to β -lactam antibiotic resistance that may be relevant to understanding the variables that influence *P. aeruginosa* evolution in complex environments, including infections.

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A LasR variant of *Pseudomonas aeruginosa* with a unique gene-regulation profile

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Pseudomonas aeruginosa is an opportunistic pathogen that coordinates gene expression through a cell-to-cell communication system called quorum sensing. The quorum sensing circuitry of *P. aeruginosa* consists of two acyl-homoserine lactone-responsive transcriptional regulators and their cognate signal synthases, LasR-I and RhlR-I, and a third, quinolone-regulated system, pqs. In strain PAO1, LasR-I sits at the top of the quorum sensing hierarchy, acting on RhlR-I through activation of rhII and on pqs through its regulator PqsR. The dominance of the Las circuit observed in PAO1 is partially attributed to an inactivating mutation in *mexS*, the product of which serves as a suppressor of the transcription factor MexT. MexT upregulates the efflux pump MexEF-OprN, overexpression of which results in reduction of some Rhl-regulated extracellular factors, including proteases. When PAO1 is continually grown in casein, a medium that requires a quorum sensing-regulated protease for carbon and energy, enrichment of *lasR*-null mutants is common, reproducibly comprising up to 30% of the final population. We hypothesized that the *mexS* mutation contributes to cooperative behaviors when quorum sensing is required, and tested this by passaging PAO1, *mexS*-restored PAO1 and a *mexT* deletion mutant on casein for 30 days. Unexpectedly, we found that *mexS* restoration destabilized cooperation, and cultures failed to propagate by ~15 days. Additionally, *mexT*-null and *mexS*-restored populations exhibited selection for a partially functional *lasR* variant, LasR-V226I. Unlike a *lasR*-null mutant, LasR-V226I retains activity of some Rhl-regulated genes and has higher expression of *pqsA*, a *pqs* gene required for quinolone synthesis. V226I has a significant competitive advantage when cocultured with wildtype PAO1 in casein. This variant lends insight into paths of alternative quorum sensing regulation under conditions requiring cooperation.

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Diversity and Distribution of LuxI/R Quorum Sensing Systems in Proteobacteria

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Among the diverse mechanisms of bacterial inter-cellular communication, quorum sensing (QS) remains one of the most extensively studied. In Proteobacteria, the canonical QS system involves the LuxI/LuxR module, where LuxI synthesizes N-acyl-homoserine lactones (AHLs) and LuxR regulates gene expression in response to AHLs. Despite extensive characterization in model organisms, the distribution, genomic organization, and taxonomic comprehensiveness of canonical LuxI/R systems remains unexplored.

Here, we present the first large-scale, genome-wide assessment of LuxI/R QS systems across 30,000+ publicly available genomes and manually curated spanning 938 genera within the Alpha, Beta, and Gammaproteobacteria. Using pfam-based domain annotation, we mapped the occurrence, copy number, and synteny of LuxI/R homologs. LuxI/R systems were identified in ~68% of genera, with evident enrichment in symbiotic, plant-associated, and opportunistic taxa such as *Rhizobium*, *Burkholderia*, *Pseudomonas*, and *Vibrio*. Conversely, entire genera, including *Escherichia*, *Salmonella*, and *Klebsiella*, lacked LuxI/R systems, suggesting evolutionary loss, niche-specific signaling strategies, or reliance on alternative currently unknown communication pathways.

Our results also reveal genera with multiple, non-redundant and sometimes taxonomically not-related LuxI/R pairs per genome, indicating modular architectures and horizontal gene transfer events and genetic arrangements. This suggests that distinct QS systems are often acquired in response to specific ecological pressures, highlighting their role as adaptable regulatory tools that enhance bacterial fitness and competitiveness across diverse environmental niches. Finally, we have developed a web platform (LUXOME) that identifies the presence of the LuxI/R systems in publicly available genomes. Additionally, users can upload their own genomic data to screen for the presence of LuxI/R systems.

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Quantitative physiology and cell-cell communication in *Burkholderia glumae*

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Bacterial cell–cell communication via extracellular auto-inducing signals (often referred to as “quorum sensing”) is often considered primarily a cell-density regulatory switch (Platt and Fuqua, 2010). This view is quite restrictive with respect to the physiological and ecological potential of cell–cell communication (Spacapan et al., 2023).

In natural contexts, most bacterial populations experience variable environments. In such environments, cell–cell communication depends on the concentration of the auto-inducing signal, which also varies, thereby affecting population growth. The physiological state of a cell (e.g., its growth rate) influences auto-inducing signal production, which in turn affects the physiological state.

We aim to disentangle the effect of the signal on growth from the effect of growth on signal production. We carefully quantify signal production in constant environments across different nutrient conditions, as well as the effect of signal concentration on growth rate. By combining these measurements with proteome allocation constraints (Scott and Hwa, 2023), we aim to formulate a comprehensive quantitative model of the physiology of signal production and sensing.

We chose *Burkholderia glumae* as a model organism. It has an acyl-homoserine lactone (AHL) type of cell–cell communication system, which is widespread among Gram-negative bacteria and has been shown to slow bacterial metabolism (An et al., 2014). Additionally, the *B. glumae* strain “AU6208” was isolated from a human clinical sample but still retains the ability to cause rice blight (Devescovi et al., 2007). Therefore, studying this particular cell–cell communication system can provide insights into its role in both clinical and ecological contexts.

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Inter-species communication? Cystic fibrosis airway-associated pathogens display strong signatures of adaptation in a polymicrobial lung infection model

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People with cystic fibrosis (CF) frequently suffer from chronic airway infections. Complications from these infections are detrimental to quality of life and remain a leading cause of mortality. These airway infections are often polymicrobial in nature, with multiple species of Gram-negative and Gram-positive bacteria, and fungi co-colonising the airway niche. Key species observed at high frequency in the CF airways, or species associated with worsened pulmonary health include the WHO-designated 'high priority' pathogen *Pseudomonas aeruginosa* (Gram-negative), *Staphylococcus aureus* (Gram-positive), *Stenotrophomonas maltophilia* (Gram-negative), and *Candida albicans* (fungus). Populations of these microbes within the CF airways are rarely homogenous, and amongst the intra-species variants that co-habit this niche, certain mutations are observed at higher frequency than expected under genetic drift. The over-representation of these genotypes suggests that these mutations are 'pathoadaptive' – that they increase fitness in the airway environment. However, we still have little idea as to why this is. One possibility is that these 'pathoadaptive' mutations influence the interactions between different microbial species, yet their impact on the ecological dynamics of the microbial community remains under-explored. In this study, we used genomic analyses to explore the mutational dynamics of several CF-associated species, including both laboratory strains and clinical isolates, when cultured in nutritional conditions mimicking the CF lung. We also investigated the adaptive response(s) to growth in polymicrobial culture, utilising an in vitro experimental system that allows stable co-culture of several airway-associated microbes over long periods of time. The data reveal clear signatures of adaptation to the CF airway environment in both laboratory and clinical isolates, and furthermore, that these adaptations have major consequences on the fitness of the strains and on the ecological dynamics of the polymicrobial community.

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Functional Analysis of Three Quorum Sensing Systems in *Burkholderia plantarii*, the Causal Agent of Rice Seedling Blight

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Numerous gram-negative bacteria regulate the expression of virulence factors through quorum sensing (QS) mediated by acylhomoserine lactones (AHLs). In plant-pathogenic, gram-negative bacteria, QS regulates key pathogenic traits, including toxin production, biofilm formation, and swarming motility. *Burkholderia plantarii*, the causal agent of rice seedling blight, possesses three QS gene pairs, *plal1/plaR1*, *plal2/plaR2*, and *plal3/plaR3*. Although the *plal1/plaR1* system has been previously characterized, the functions of the other two QS systems remain unclear. In this study, we generated QS-deficient mutants of the *B. plantarii* type strain MAFF 301723 to investigate the roles of each QS gene pair in AHL biosynthesis and regulation of virulence factors.

The *plal1/plaR1*-QS system seems to be the primary QS regulatory pathway in MAFF 301723 and utilizes N-octanoyl-L-homoserine lactone (C8-HSL) to regulate swarming motility. In contrast, the *plal2/plaR2* system did not regulate any general function, although *Plal2* was found to be capable of producing N-3-hydroxydecanoyl-L-homoserine lactone (3-OH-C10-HSL). Notably, the *plal3/plaR3* system plays a crucial role in the biosynthesis of the phytopathogenic toxin tropolone through the production of putative AHL, N-hexadecanoyl-L-homoserine lactone with two double bonds (C16:2-HSL) by LC-MS/MS analysis. These findings suggest that multiple QS systems collectively contribute to the complex virulence regulation of *B. plantarii*, providing new insights into the development of QS-targeted biocontrol strategies in agriculture.

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Interkingdom Signaling between *Bacillus subtilis* and *Sporisorium scitamineum*: Exploiting the Ecological Role of Natural Product as Novel Biocontrol Agents

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Global food security challenges demand innovative crop protection approaches that harness natural microbial interactions. We propose to investigate interkingdom cell-cell communication between beneficial bacteria (*Bacillus subtilis* species complex) and the fungal pathogen *Sporisorium scitamineum*, which causes devastating sugarcane smut disease. While bacterial lipopeptides are recognized for antimicrobial properties, their role as intercellular signaling molecules at sub-inhibitory concentrations remains unexplored for basidiomycete plant pathogens.

We hypothesize that bacterial lipopeptides modulate fungal cell-cell communication at concentrations below antimicrobial thresholds. Our theoretical framework suggests these compounds target signaling pathways involved in mating recognition, morphological switching, and virulence expression. We anticipate transcriptomic and metabolic analyses will reveal alterations in genes associated with cell surface receptors, secondary metabolite production, and stress responses, suggesting bacteria can hijack fungal communication systems. This interdisciplinary approach integrating bacterial communication with fungal biology and agricultural science is expected to challenge traditional paradigms by demonstrating antimicrobial compounds function as communication tools in microbial communities. Our theoretical framework suggests significant implications for sustainable agriculture, revealing how bacterial natural products, including signaling compounds extends beyond intraspecies communication influence interkingdom interactions.

"Cell-cell communication in bacteria: new insights and future trends"

28-30 October 2025 | Trieste, ITALY

AHL-specific global gene regulation by a promiscuous receptor in *Chromobacterium subtsugae*

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Acyl-homoserine lactone (AHL) quorum sensing enables bacteria to sense and respond to changes in population density. These systems involve an AHL synthase and a receptor that functions as a transcription factor. Upon AHL binding, the receptor undergoes a conformational change that enables interaction with a conserved recognition sequence in the promoter of its gene targets, activating dozens of genes. AHL-receptor interactions are generally thought to be selective, ensuring kin-specific communication. However, some receptors respond to a broader range of AHLs, raising the possibility of interspecies crosstalk. Previous studies of promiscuous receptors suggest native AHLs elicit similar but more robust gene activation than non-native AHLs, but most have focused on one or a few gene targets. How non-native AHLs impact broader gene expression remains an open question. Here, we investigated this question using the soil bacterium *Chromobacterium subtsugae*, which encodes a single AHL receptor, CviR. CviR responds to both its native signal, C6-HSL, and non-native signals such as C8-HSL. Using transcriptomics, we compared gene expression in response to these two AHLs and found that each activates overlapping but distinct regulons. We generated dose-response experiments with selected gene targets and found gene-specific differences in sensitivity to each AHL, with some promoters more strongly activated by C6-HSL and others by C8-HSL. Similar gene-specific responses were observed in a heterologous host expressing CviR, suggesting differential activation is due to CviR. Our findings support a model in which different AHLs elicit distinct CviR conformations that bias promoter sequence preference and/or transcriptional output. This study highlights how receptor promiscuity may allow bacteria to alter gene expression when non-native AHLs are detected, potentially enabling flexible behavioral responses in polymicrobial communities.

"Cell-cell communication in bacteria: new insights and future trends"

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Elucidating RNA-RNA interaction networks of *Pseudomonas aeruginosa* during interbacterial interactions

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Interbacterial interactions play a crucial role in shaping bacterial communities, significantly impacting bacterial physiology. *Pseudomonas aeruginosa*, a common pathogen found in human microbial communities, poses a serious threat to immunocompromised individuals due to its ability to cause severe infections. Exploring the interbacterial interactions of *P. aeruginosa*, particularly through small regulatory RNA molecules (sRNAs), is vital for advancing infection treatments and understanding bacterial behavior in complex environments. Our primary objective is to define the sRNA interaction network that occurs in *P. aeruginosa* during its interactions with other bacteria and to decode the regulatory roles these sRNAs play in these interactions. To this end, we applied RIL-seq, a method to map RNA-RNA interactions on a global scale, to study RNA pairs in *P. aeruginosa*, comparing pure cultures to those exposed to *Staphylococcus aureus* (*S. aureus*) spent medium. We mapped the sRNA interaction network in *P. aeruginosa*, revealing sRNA interactions that may participate in the bacterial response to *S. aureus* presence. We also discovered and validated several novel sRNAs. Among the novel sRNAs identified, a particularly promising sRNA with several intriguing targets is SasA. SasA was strongly induced and was found to have more regulatory interactions with its targets upon exposure to *S. aureus* spent medium. SasA targets genes involved in motility, biofilm formation, and adherence in *P. aeruginosa*—all critical factors contributing to virulence and pathogenicity. Our experiments revealed that SasA is regulating the production of pyocyanin, a potent virulence factor responsible for cell death in cystic fibrosis (CF) patients. Pyocyanin production is closely associated with the initiation of virulence mechanisms in *P. aeruginosa*. Further experiments indicate that SasA affects motility and biofilm formation. Understanding the relationship between SasA, pyocyanin production, motility and biofilm formation, could be pivotal in developing treatments that reduce or prevent these virulent traits of *P. aeruginosa*.

"Cell-cell communication in bacteria: new insights and future trends"

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Investigating AHL-responsive LuxR Solos in *Pseudomonas* spp.

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Quorum sensing (QS) allows bacteria to act as multicellular organisms by regulating gene expression of community behaviors such as biofilm formation and the production of virulence factors. The canonical QS relies on paired LuxI synthases and LuxR receptors working together as cognate partners, producing and responding to AHLs; however, many bacteria harbor orphaned LuxR receptors, LuxR solos, that lack their cognate LuxI partners. This sub-family of regulatory proteins represent evolutionary puzzles, potentially responding to exogenous AHLs from neighboring bacteria or novel type of unknown molecules.

A phylogenetic in silico analysis, combined with functional grouping based on primary structure and genomic context, suggests that certain LuxR solos may be responsive to AHLs produced by other bacterial species in the same environment. However, the specific AHL ligands and regulatory mechanisms remain largely uncharacterized. This study investigates LuxR solos from two phylogenetically distinct *Pseudomonas* species, *P. protegens* and *P. mosselii*, both of which lack a complete QS system but encode likely AHL-binding LuxR solo candidates. Using a comprehensive screening approach, nine luxI promoters, each containing experimentally validated lux boxes and derived from diverse bacterial strains, were individually introduced into both *Pseudomonas* hosts. Transcriptional activity was assessed following exposure to AHL cocktails, enabling the detection of cross-species AHL–LuxR solo interactions through a positive feedback mechanism.

Future work will involve targeted mutagenesis of the LuxR solo genes, comparative analysis between wild-type and mutant strains, and heterologous protein expression to characterize ligand-binding specificity. This study aims to determine the function of the LuxR solos in the inter-species signalling in the plant microbiome.

"Cell-cell communication in bacteria: new insights and future trends"

28-30 October 2025 | Trieste, ITALY

THE QUORUM SENSING INHIBITOR QSTATIN DECREASES THE VIRULENCE OF PATHOGENIC VIBRIOS BELONGING TO THE HARVEYI CLADE

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Vibrios belonging to the Harveyi clade (including *V. harveyi* and closely related species, such as *V. campbellii* and *V. parahaemolyticus*), are among the most significant pathogens in aquaculture. The traditional strategy to control bacterial disease in aquaculture is to use antibiotics. However, the effectiveness of antibiotics is rapidly decreasing as a result of the emergence and spread of (multiple) antibiotic resistance. Therefore, for the sustainable development of the aquaculture industry, there is an urgent need for novel strategies to control bacterial infections. Quorum sensing (QS) interference in Harveyi clade vibrios has been shown to reduce virulence without killing or inhibiting bacterial growth, thereby offering a promising alternative to conventional antimicrobials. The small molecule Qstatin (1-(5-bromothiophene-2-sulfonyl)-1H-pyrazole) was previously documented to reduce the virulence of *V. vulnificus* by affecting the activity of SmcR, the master regulator of its three channel QS system. Since the three channel QS system is required for full virulence of Harveyi clade vibrios, we reasoned that Qstatin might be an interesting virulence inhibitor to control disease caused by these bacteria as well.

We found that 20 μ M Qstatin inhibited QS-regulated bioluminescence and swimming motility (a major QS-regulated virulence factor) of *V. campbellii*, without affecting growth in nutrient-rich growth medium nor survival in nutrient-poor conditions. Further, we found that Qstatin protected gnotobiotic brine shrimp larvae from 12 pathogenic strains belonging to the species *V. parahaemolyticus*, *V. harveyi* and *V. campbellii*.

This study thus demonstrates that Qstatin is an effective quorum sensing inhibitor of Harveyi-clade vibrios. The characteristic that it shows a significant antivirulence effect but does not directly kill bacteria indicates that it can be regarded as a novel therapeutics in order to control infections caused by Harveyi clade vibrios in aquaculture.

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A horizontal banner with a green border. The left side features a microscopic image of various bacteria, including spherical and rod-shaped cells. The right side shows a blurred background of a building and a crowd of people.

"Cell-cell communication in bacteria: new insights and future trends"

28-30 October 2025 | Trieste, ITALY

What we do

According to its mandate, the ICGEB:

- Promotes international **scientific collaboration**, cooperation and **diplomacy**
- Conducts **advanced research** in the laboratories in Trieste, New Delhi, and Cape Town
- Awards **Fellowships** for PhD students and researchers to develop research skills
- Organises and sponsors **meetings and workshops** on cutting-edge topics in Life Science
- Supports research in Member States by **funding** projects of excellence in collaboration with ICGEB labs
- **Transfers technology** and know-how to biotech companies
- Assist Countries to enhance national capacities in the **regulation of biotechnology** and its products

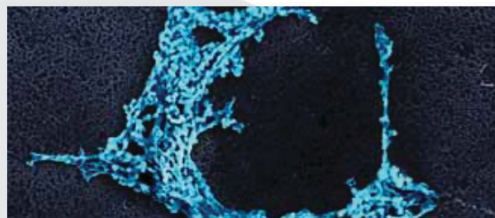
Research

The ICGEB laboratories number 44 and offer a scientific environment of the **highest international standard** and are equipped to carry out the most advanced experimental research in molecular and cellular biology.

In **Trieste** 200 people representing over 30 nationalities, pursue biomedical research including projects on cardiovascular, neurodegenerative and infectious diseases, immunology and human genetics, and the development of new treatments based on gene and stem cell therapy and the production of biopharmaceuticals as well as research on plant biotechnology.

In **New Delhi** the groups conduct research in mammalian and plant biology, focusing on the development of diagnostic and vaccine candidates for malaria, hepatitis and dengue, along with advanced research on plant biotechnology and biofuels.

In **Cape Town**, more than 60 researchers investigate infectious (HSHV/ parasitic disease and plant biotechnology), non communicable diseases (cancer) and biopesticides.



Governance

The ICGEB **Board of Governors** comprises a representative from each Member State and meets once a year. The **Scientific Council** includes Nobel laureates, who support scientific activities and makes recommendations to the Board.



Fellowships, Meetings and Courses

ICGEB offers postgraduate and postdoctoral **Fellowships** to scientists from its Member States; an international PhD Course is run in all three ICGEB laboratories in collaboration with prestigious academic institutions.

An average of over 30 practical and theoretical **Meetings** and **Courses** are organised every year on subjects at the forefront of biomedical research and biotechnology applications, with over 1200 researchers participating each year.



Technology Transfer

One of the key objectives of ICGEB is the **transfer of technologies** to biotech companies. To date, the Centre has concluded over 80 agreements with industrial partners in Argentina, Brazil, China, Cuba, Egypt, UAE, India, Iran, Pakistan, South Africa, Sri Lanka, Turkey, Uruguay, USA and Venezuela, predominantly to produce pharmaceuticals obtained through genetic engineering (insulin, erythropoietin, interferon and different growth factors), diagnostic kits (celiac disease) and vaccines (malaria and dengue).



Regulatory Science

The Organisation is active in providing advisory services and technical assistance to government officials and their experts in Member States, helping them to devise and implement effective biosafety policies, legislation and administrative systems governing the **safe and sustainable use of modern biotechnology** and its products. Current projects are active in sub-Saharan Africa and the Latin America and Caribbean Region, and are funded by major philanthropic foundations and multilateral organisations.

Funding

The Centre is funded by the governments of over 60 countries. The main contribution is provided by the **Government of Italy** through the Ministry of Foreign Affairs and International Cooperation (MAECI), followed by the **Governments of India** and **South Africa**, the three countries that host the Centre's laboratories.

Other Member States include the BRICS, least developed countries and emerging economies in Asia, South America and Africa.

Besides the core budget for institutional activities, the ICGEB is recipient of grants from government agencies, charities, non-profit foundations and the private sector.

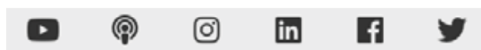
At all three ICGEB locations specific research projects have been awarded funding from the European Commission (including the European Research Council); the Wellcome Trust, Bill&Melinda Gates Foundation, the Royal Society and the AICR, UK; the JDRF, the NIH, and the Leukemia & Lymphoma Society, USA; the Canadian Grand Challenges Scheme, Canada, the AXA Foundation and AFM, France.

Funds for the ICGEB laboratories are also provided by national government bodies, charities and foundations, including the MIUR, Regione Friuli Venezia Giulia, Telethon, AIRC, ISS and various banking Foundations in Trieste; the Department of Biotechnology of the Indian Government in New Delhi, and the National Research Foundation and Medical Research Council of South Africa in Cape Town.

Outreach

ICGEB Communications, Public Information and Outreach works to ensure the visibility of the Organisation, its activities, and its **dissemination of scientific information** to a range of audiences through digital communications, **Engagement activities, Publications and Media relations.**

ICGEB is active on Social media. To promote advocacy and fundraising, we work to consolidate the **ICGEB Alumni Association** that constitutes over 3000 former scientists.



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