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The role of AI-2-mediated quorum sensing in gut microbiome-immune dysbiosis

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Microbes colonize the gastrointestinal tract, forming microbiomes essential for gut function, immune responses, and other host systems[1]. Patients requiring life-support treatment develop profound gut microbiome ecology alterations, characterized by a loss of beneficial commensals and overgrowth of potential pathogens (pathobionts), including *Enterobacteriaceae* and *Enterococcaceae* families[2,3]. This increases patients' risk of adverse outcomes, including nosocomial infections, by driving systemic immune dysregulation[4,5]. Prior research suggests that inter-microbe molecular communication (quorum sensing) contributes to pathobiont overgrowth in ICU patients' guts[6,7]. The quorum-sensing molecule AI-2 contributes to gut microbiome dysbiosis, yet its role in critical illness is poorly understood[8,9]. This project aims to understand the contribution of altered *Enterobacteriaceae* AI-2 signalling towards gut microbiome dysbiosis and host immune dysfunction in critical illness. We will screen a library of ICU-patient-derived *Enterobacteriaceae* isolates and bioreactor-cultured fecal microbiomes against healthy human-derived samples to assess AI-2 concentration and activity. Next, we will utilize AI-2-deficient mutant bacteria and over-expressing controls to test whether AI-2 enables pathobiont overgrowth in germ-free and gnotobiotic mice. Lastly, we will use patient isolates and mutants to determine the impact of AI-2 on the host immune response to ICU gut microbiome dysbiosis in gnotobiotic mice. Through this, the effects of AI-2 signalling on pathogenic gut bacteria colonization resistance, inflammation, and patient outcomes will be defined. Our results will provide a mechanistic understanding of the role of gut dysbiosis in adverse outcomes in ICU patients and inform the development of targeted treatments or biomarkers for this patient population.

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Background

- Profound gut microbiome alterations, especially overgrowths of *Enterobacteraiceae* and *Enterococcus species,* are common amongst patients in the ICU[1]
- Pathological gut alterations increase patients' risks of adverse outcomes through driving systemic immune regulation[1]
- Quorum sensing is a modulator of the gut microbiome and may influence pathobiont overgrowth in the guts of ICU patients[2, 3]
- AI-2, the most ubiquitous quorum-sensing molecule, has been linked to disease-associated dysbiosis, but its connection to critical illness is understudied[4]

Hypothesis:

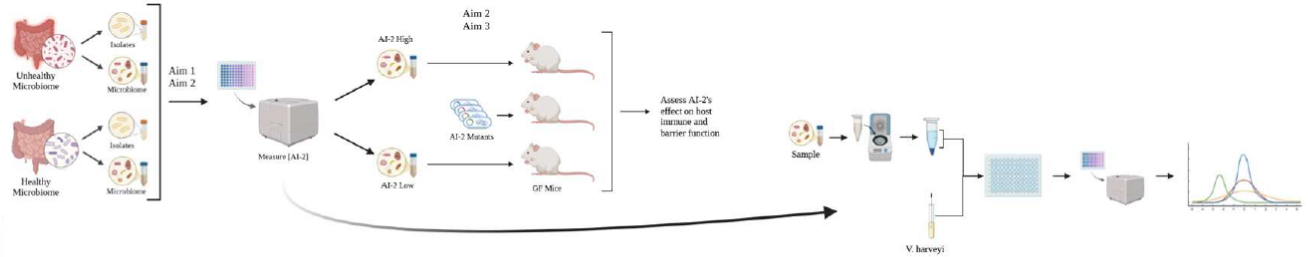
Pathobiont *Enterobacteriaceae* in the gut microbiome of critically ill patients overexpress AI-2, leading to their overgrowth and contributing to systemic immune dysregulation.

Aims

1. Characterize AI-2 production by gut pathobiont Enterobacteriaceae in the microbiome of critically ill patients.
2. Determine the contribution of AI-2 quorum sensing towards *Enterobacteriaceae* dominance in the gut microbiome of critically ill patients.
3. Determine the impact of gut AI-2 quorum sensing on mucosal barrier and systemic immune dysfunction.

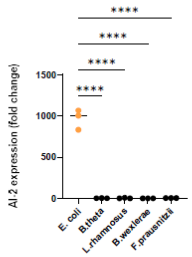
Research Approach

- Compare AI-2 production in bacterial isolates and microbiomes between healthy and dysbiotic states.
- Investigate the association between AI-2 and colonization efficiency of pathobionts.
- Investigate the impact of AI-2 on host responses.

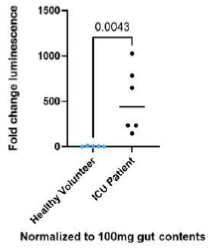


Results and Future Directions

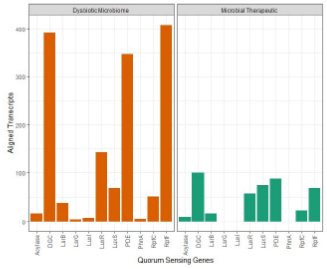
AI-2 is increased in pathobionts compared to commensal bacteria



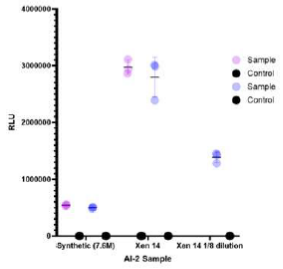
AI-2 is increased in ICU gut microbiomes



AI-2 associated gene expression is altered in unhealthy gut microbiomes



Pathobionts produce high quantities of AI-2



Conclusion

- Gut dysbiosis in critical illness contributes to adverse outcomes including immune dysfunction and infection.
- This study aims to determine mechanistic underpinnings of this core aspect of critical illness pathogenesis contributed by Ai-2 quorum sensing.
- Understanding mechanistic drivers of dysbiosis in critical illness will enable rationally designed, mechanism-informed approaches to treatment to improve outcomes in this vulnerable patient population or inform biomarker-based analysis.

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