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University of Maryland School of Medicine Researchers Generate Extensive Transcriptome Data Atlas of *Streptococcus pneumoniae* Host-Pathogen Interactions

A comprehensive resource for the pneumococcal field that includes generalized as well as bacterial- and/or organ-specific pathogen and host gene expression profiles, opening novel avenues for vaccines and therapeutics

BALTIMORE, December 14, 2020 – Researchers at the University of Maryland School of Medicine and their collaborators published one of the most comprehensive transcriptome analyses on five host body sites and three distinct bacterial strains of *Streptococcus pneumoniae* during infection in the *Proceedings of the National Academy of Sciences U.S.A.* today. This transcriptome map provides invaluable new information about the host and pathogen interactions during pneumococcal colonization and disease that will help researchers better treat infections by this pathogen. Link to study

The Gram-positive microbe *S. pneumoniae* asymptomatically colonizes the nasopharynx and is also an opportunistic pathogen which commonly infects young children, immunodeficient patients and the elderly. With the advancement of antibiotics and the introduction of the first pneumococcal conjugate vaccine in 2000, deaths attributable to *S. pneumoniae* have declined. However, increasing antibiotic resistance and serotype replacement have been observed and pneumococcal infections continue to be a significant cause of morbidity and mortality.

The University of Maryland School of Medicine researchers, working with collaborators at the University of Alabama at Birmingham and Yale University School of Medicine, analyzed bacterial and host gene expression focusing on five body sites of a mouse model – the nasopharynx, heart, blood stream, lung and kidney, using three diverse strains of *S. pneumoniae*. These critical comparisons provide valuable insights into the mechanisms underlying colonization versus disease and infected versus uninfected host. This atlas conclusively demonstrated the ways in which the host and bacteria gene expression profiles during colonization differ from those at multiple host infection sites.

This was the first time that such specific responses were mapped out from both the host and pathogen perspectives, and the investigators found, for instance, which *S. pneumoniae* genes were always highly expressed at all anatomical sites; ideally being optimal targets for vaccine or therapeutic intervention. The investigators did not stop at the descriptive analysis of the transcriptomes but went further and confirmed their findings using bacterial mutants and *in vivo*

challenge experiments and host treatments. Their research demonstrated that interferon beta treatment allowed the host to sequester the infection away from key organs. This promoted host survival and provided insights into potentially new avenues for treatment.

This atlas is a valuable resource for researchers who are working toward eradicating *S. pneumoniae* infections and serves as powerful new approach for other investigators working with other bacteria pathogens.

Hervé Tettelin, PhD, Professor, Department of Microbiology and Immunology, Institute for Genome Sciences, University of Maryland School of Medicine was the Principal Investigator on the project. He rationalized that *"By addressing the large diversity, or pan-genome, observed among isolates of the pneumococcus, by capitalizing on robust mouse models of colonization and disease, and by performing very large-scale transcriptomics at five anatomical sites in vivo, we could identify and experimentally verify bacterial determinants required to cause disease, as well as host pathways turned on in response to infection. Thanks to our highly collaborative work at three institutions and support from Merck, we now have in hand novel potential vaccine candidates that are highly expressed and therefore targetable at all diseased anatomical sites, and we revealed host pathways that we may be able to modulate to help the host mount a better protective response against infection."*

Dr. Tettelin co-designed the study with Carlos J. Orihuela, PhD, from the University of Alabama at Birmingham. *"S. pneumoniae is a leading cause of infectious death worldwide. Understanding what occurs inside an infected individual is paramount if we want to create better vaccine and therapeutics. The performed work is the most comprehensive analyses of S. pneumoniae in vivo gene expression performed to date. Moreover, we also have the host gene response across vital organs. Our hope is that this data, which shows how the pneumococcus and host are responding to one another, will serve as a key resource for other laboratories that are working towards preventing S. pneumoniae disease"* said Dr. Orihuela.

Ellen Foxman, M.D., Ph.D., Assistant Professor of Laboratory Medicine and Immunobiology, Yale School of Medicine said of her work performing data analyses for the project: "*It was a privilege to participate in this collaborative project, which brought together scientists from diverse areas of expertise to develop a comprehensive atlas of the body's interactions with an important human pathogen*."

"*The fact that interferon treatment promoted host survival provided us with important insights into potentially new avenues for treatment*," said study co-author Adonis D'Mello, a graduate student in molecular medicine in Dr. Tettelin's laboratory at the Institute for Genome Sciences, who performed the bioinformatic analyses that highlighted pathways of host-pathogen interactions. "*We were able to build upon analytical pipelines to provide a more comprehensive way of studying diverse systemic pathogens.*"

Ashleigh Riegler, Eriel Martinez, Sarah Beno, and Tiffany Ricketts from the University of Alabama at Brimingham, performed experiments and participated in data analyses.

Funding was provided through the Merck Investigator Studies Program that supports hypothesis-generating clinical and pre-clinical research that is initiated, designed and implemented by external investigators. Dr E. David G. McIntosh MBBS MPH LLM PhD, Executive Director Scientific Affairs (Vaccines) MSD, said, "*Merck acknowledges the importance of these fundamental scientific discoveries, congratulates the investigators on their painstaking work and reiterates our commitment to support independent scientific research*."

This project was also supported with funds from the National Institutes of Health, National Institute of Allergy and Infectious Diseases under award R01AI114800 to Drs. Orihuela and Tettelin.

About the University of Maryland School of Medicine

Now in its third century, the University of Maryland School of Medicine was chartered in 1807 as the first public medical school in the United States. It continues today as one of the fastest growing, top-tier biomedical research enterprises in the world -- with 45 academic departments, centers, institutes, and programs; and a faculty of more than 3,000 physicians, scientists, and allied health professionals, including members of the National Academy of Medicine and the National Academy of Sciences, and a distinguished two-time winner of the Albert E. Lasker Award in Medical Research. With an operating budget of more than $1.2 billion, the School of Medicine works closely in partnership with the University of Maryland Medical Center and Medical System to provide research-intensive, academic and clinically based care for nearly 2 million patients each year. The School of Medicine has more than $540 million in extramural funding, with most of its academic departments highly ranked among all medical schools in the nation in research funding. As one of the seven professional schools that make up the University of Maryland, Baltimore campus, the School of Medicine has a total population of nearly 9,000 faculty and staff, including 2,500 student trainees, residents, and fellows. The combined School of Medicine and Medical System ("University of Maryland Medicine") has an annual budget of nearly $6 billion and an economic impact more than $15 billion on the state and local community. The School of Medicine faculty, which ranks as the 8th highest among public medical schools in research productivity, is an innovator in translational medicine, with 600 active patents and 24 start-up companies. The School of Medicine works locally, nationally, and globally, with research and treatment facilities in 36 countries around the world.
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