UM School of Medicine Receives $7.5 Million Grant to Create Complex Model of Female Reproductive Tract to Study Infections

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Research Will Help Identify Mechanisms by Which the Microbiome Affects the Susceptibility to Sexually Transmitted Infections

Researchers at the Institute for Genome Sciences (IGS) at the University of Maryland School of Medicine have received a $7.5 million federal grant to create a complex model of the female reproductive system in order to study sexually transmitted infections (STIs). They plan to create a realistic 3D model that integrates vaginal and cervical epithelial cells and the bacteria that colonize these cells, called a microbiome. They aim to use this model to identity factors that play a role in chlamydia and gonorrhea infections experienced by a growing number of women in the U.S. and worldwide.

The grant was awarded to principal investigator **Jacques Ravel, PhD**, Professor of Microbiology and Immunology at UMSOM and Associate Director of UMSOM's IGS. His co-principal investigators will be long-time collaborator and chlamydia expert, **Patrik Bavoil, PhD**, Professor of Microbial Pathogenesis at University of Maryland School of Dentistry, and J**ason Gleghorn, PhD**, Associate Professor of Biomedical Engineering at the University of Delaware. Over the course of the 5-year grant, the research team will build the 3D model to study how STI's take hold and spread, mimicking infections that affect the reproductive tract.

Constructing the 3D model will require several feats of biomedical engineering. These include growing all cell types from vaginal and cervical tissue biopsy samples collected from research volunteers, coaxing the cervical cells to produce a critical protective mucus layer, and adding colonies of thriving bacteria to recreate the microbiome found at both of these anatomical sites. Dr. Ravel is a world-renowned expert on the role of the genital microbiome in female reproductive health.

"We are trying to mimic as much as possible what occurs naturally in the female reproductive tract," said Dr. Ravel. ***"We cannot look at cells on a fixed slide under a microscope to determine how infections take hold and persist in the body. We need to understand how these cells interact with the microbiome to determine***

whether a pathogen gains entry to the body or is destroyed by the immune system."

Chlamydia is the most frequently reported sexually transmitted infectious disease in the United States, according to the **Centers for Disease Control and Prevention**. Many women experience repeated or persistent infections, which can ultimately lead to pelvic inflammatory disease and infertility. Gonorrhea can present similar complications if infections persist.

"We have so many unanswered questions when it comes to understanding why some patients can clear these infections naturally or with a course of antibiotics, while others cannot," Dr. Ravel said. ***"We would like to map out how healthy cells in the reproductive tract interact with the microbiome and how that interaction prevents or facilitates the infection, which has not been done before."***

Current models do not integrate the presence of the microbiome. ***"It is logical to hypothesize that the interaction between cells and these colonies of bacteria plays a critical role in infection outcomes,"*** Dr. Ravel said, "***but we do not know for certain until we test this theory in our new model, as we cannot do that in vivo. This is a major innovation in this project."***

The research ultimately aims to improve the understanding of STI infection progression, resistance to treatment, and susceptibility to new infections. Over time, such findings may lead to improved approaches to manage STIs, including testing new probiotic treatments. These preclinical studies are often required by the Food and Drug Administration before experimental treatments can be tested in patients. The model could replace the inadequate animal models currently used, Dr. Ravel said. None of these reproduce the unique microbial ecosystem found in a female genital tract.

"We plan to use technological genomics and bioinformatics platforms developed at IGS and apply system biology approaches in order to gain a fuller understanding of the interactions between reproductive cells, the microbiome, and invading pathogens," Dr. Ravel said***.***

The large project grant is funded by the National Institutes of Health (1U19AI158930 and includes collaborations with the University of Virginia School of Medicine.

"Our leading genomics researchers at IGS aim to improve our understanding of the mechanisms by which the microbiome affect human reproductive health, and translate this knowledge into novel therapeutics measures to modulate the microbiome and optimize women's health in the US and worldwide," said E. Albert Reece, MD, PhD, MBA, Executive Vice President for Medical Affairs, UM Baltimore, and the John Z. and Akiko K. Bowers Distinguished Professor and Dean, University of Maryland School of Medicine. *"As IGS investigators apply the tools of genomic analysis to medical challenges, the impact of this research is far-reaching and could potentially help millions of women who suffer from not only serious sequalae from sexually transmitted infections but also poor reproductive health outcomes such as preterm birth."*

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