Abigail Sloan Devlin, Ph.D.
Associate Professor
Dept. of Biological Chemistry and Molecular Pharmacology
Harvard Medical School

250 Longwood Avenue
Seeley G. Mudd Building, Room 622B
Boston, MA 02115
Cell: 860-449-4689
sloan_devlin@g.harvard.edu

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Dear Members of the HMS-SNUH-SNUCM Review Committee,

I am writing to express my intent to apply for a grant from the Harvard Medical School – Seoul National University Hospital – Seoul National University College of Medicine Collaborative Research Program.

Proposal Title: Investigating causal links between the gut microbiome and postpartum depression
Lead PI: Devlin, Sloan, sloan_devlin@g.harvard.edu, Biological Chemistry and Molecular Pharmacology, Harvard Medical School
SNUH/SNUCM PI (if known): *I will need help identifying an SNUH/SNUCM PI.* A good match would either be an OB/GYN who has access to clinical samples or a neuroscientist who has lab members who can perform mouse behavior experiments. If the latter, I could partner with Dr. McElrath (below) to obtain the human fecal samples locally, through BWH.
Co-PI (*note, still need to confirm participation*): McElrath, Thomas, tmcelrath@bwh.harvard.edu, Center for Fetal Medicine and Prenatal Genetics, Brigham and Women's Hospital
Estimated Total Amount to be Requested: $500,000 ($250,000 per year for 2 years)

Proposal Overview: Pregnancy is a crucial part of human life and can dramatically affect the health and well-being of the mother. However, despite advances in modern medicine, the effects of pregnancy on women's health, especially mental health, remain poorly understood. In particular, postpartum depression (PPD) remains a substantial worldwide health problem. This condition affects 1 in 7 women following childbirth. There is currently a lack of understanding of how and why PPD develops, limiting the ability to prevent and treat this condition. Significant hormonal changes occur during and after childbirth. Levels of steroids including mood-altering hormones such as progesterone increase by ten-fold or more during pregnancy and then drop precipitously after delivery. This sudden change in hormones postpartum is hypothesized to trigger depression. However, how and where in the body these hormone changes affect neurological signaling is not well understood. At the same time, it is becoming increasingly clear that bacteria in the gut influence brain function and development. In recent work, we have shown that gut bacteria produce neurosteroids including allopregnanolone, also known as brexanolone or Zulresso, an FDA-approved drug to treat PPD. We have also found that levels of allopregnanolone bacterial producers and bacterial genes are significantly higher in women during their third trimester of pregnancy compared to non-pregnant subjects (*Cell* 2024). It was previously thought that allopregnanolone was produced exclusively by the host in the brain, adrenal glands, ovaries, and placenta. Our work suggests that gut bacteria are contributing to allopregnanolone production during pregnancy. Moreover, our preliminary data show that this bacterial production of allopregnanolone improves anxiety phenotypes in mice. We hypothesize that human gut bacteria contribute to the in vivo pools of neurosteroids. Moreover, we propose that modulation of bacterial production of neurosteroids during and after pregnancy will affect neurological function and behavior in mothers, thereby providing novel means to prevent and potentially treat PPD. In this proposal, we plan to investigate these hypotheses using a combination of microbiology and chemical biology investigations, animal behavior experiments, and analyses of human samples pre- and post-pregnancy.

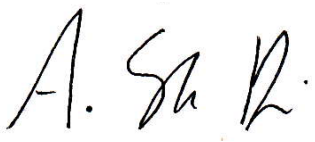
Disease area: Neuro-immunological and neurological diseases, postpartum depression

Brief description of proposed research: In Aim 1, we will investigate whether bacterial production of neurosteroids in vivo by gut bacteria affects behavior in mice, including in mouse models of PPD. To do this, we will colonize germ-free mice (housed in the HMS GF core facility) with bacterial producers of allopregnanolone and perform behavior experiments in gnotobiotic isolators. In Aim 2, we will link changes in bacteria and metabolites during and after pregnancy to PPD development in humans. We will collect and analyze deidentified longitudinal fecal and blood samples from women during and after pregnancy to track microbiome composition and steroidal metabolite levels. We will then correlate bacteria and bacterial metabolites with the development of PPD

symptoms. In Aim 3, we will identify additional steroid transformations performed by gut bacteria during pregnancy. To do this, we will culture human fecal bacterial communities and individual strains from pregnant women with steroids found in human bile and the gut during pregnancy and identify novel metabolites using mass spectrometry. The successful completion of these studies will advance our knowledge of fundamental mechanisms by which human-associated bacteria influence neural activity and behaviors. In addition, this research has significant translational implications, as identifying bacteria and bacterially produced metabolites that affect neurological phenotypes during and after pregnancy will pave the way for therapies for PPD.

Thank you for your consideration. Please let me know if you have any questions, especially with respect to partnership with an SNUH/SNUCM PI.

Sincerely,



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