Background

Chorioamnionitis is a low grade infection of the placenta. Long term consequences of chorioamnionitis in the form of asthma has been reported.[1] Not much is known about the mechanism of long term immune changes caused by chorioamnionitis in the newborn. Development of a form of immunological memory in innate immunity cells, a phenomenon known as trained immunity has been shown by Netea et.al.[2] It is possible that the trained immunity due to exposure to chorioamnionitis may contribute to the long-term consequences of chorioamnionitis.

Oxygen toxicity in the newborn is also a well-known phenomenon, causing inflammation, including lung and eye disease. Additionally, in animal models with maternal chorioamnionitis, subsequent exposure to oxygen is shown to elicit an altered response. Paradoxically, response to oxygen after exposure to endotoxin was found to be associated with some form of oxygen tolerance. The exact mechanism of this change is not certain.[3] After exposure to chorioamnionitis, if the trained monocytes are subsequently exposed to hyperoxia, it can incite an exaggerated inflammatory response and contribute to the development of Bronchopulmonary Dysplasia (BPD) in premature infants' lung.

In last summer Dr. Saurabh Gayen analyzed data provided by Dr. Zubair Aghai's Lab at Thomas Jefferson University, Philadelphia. Dr Gayen mentored a student and together they had identified that exposure to sequential chorioamnionitis and hyperoxia induces differential expression on 1646 genes and impacts key pathways involved in immune regulation and inflammation in newborns. They had also completed Ingenuity Pathway Analysis (IPA) using IPA software (Qiagen, Germantown, MD) on the 1646 differentially expressed genes in Chorio-hyperoxia group compared to control-normoxia group. The research was presented by the student in the form of a poster at Lincoln University Science Fair 2024.

Proposed Research

Dr Saurabh Gayen will be carrying out Gene Expression/Bioinformatics analysis on Peripheral Blood Monocytic Cells (PBMC) from cord blood exposed to sequential chorioamnionitis and hyperoxia. The analysis will be performed on gene expression microarray data from human neonates as well as lung samples from neonatal rat model.

Microarray data files were generated from four groups: Control-Normoxia, Control-Hyperoxia, Chorio-Normoxia and Chorio-Hyperoxia. Dr. Gayen will be focusing on Ingenuity Pathway analysis and Canonical pathway analysis using Bioinformatics tools and IPA software on the gene expression (Microarray) datasets kindly provided by Dr. Aghai.

All treatment groups will be compared to the control group using Transcriptome Analysis Console software 4.0 (TAC 4.0, Thermo Fisher Scientific, Waltham, MA). Sst-RMA normalization will be performed on cel files generated from the samples. Student t-test will be used for comparison of each treatment group with the control group. Genes with fold change ≥ 1.5 and $p \leq 0.05$ will be identified as differentially expressed. Pathway analysis will be carried out on differential gene list, using Ingenuity pathway analysis (IPA, QIAGEN Inc., https://digitalinsights.qiagen.com/IPA)[4]. IPA is one of the advanced bioinformatics tools provided by Qiagen Inc. that is a web-based

software application program for the analysis, integration, and interpretation of data derived from microarray, gene expression or other array based or sequencing methods. IPA analyses and interprets data based on the comprehensive, manually curated content of the Ingenuity Knowledge Base. IPA can identify canonical pathways, networks, toxicological functions and upstream regulators. Gene set enrichment analysis (GSEA) will also be performed on the same data set and the results will be compared with IPA analysis. Morpheus software (Broad Institute, Cambridge, MA) will be used for Cluster analysis (heat map) of differentially expressed genes.

References:

1. Getahun D, Strickland D, Zeiger RS, et al. Effect of chorioamnionitis on early childhood asthma. Arch Pediatr Adolesc Med. 2010. doi:10.1001/archpediatrics.2009.238

2. Netea MG, Quintin J, Van Der Meer JWM. Trained immunity: A memory for innate host defense. Cell Host Microbe. 2011;9(5):355-361. doi:10.1016/j.chom.2011.04.006

3. Jobe AH, Kallapur SG. Long term consequences of oxygen therapy in the neonatal period. Semin Fetal Neonatal Med. 2010;15(4):230–235. doi:10.1016/j.siny.2010.03.007

4. Kramer A, Green J, Pollard J Jr., Tugendreich S. Causal analysis approaches in ingenuity pathway analysis. Bioinformatics. 2014; 30:523–30. doi: 10.1093/bioinformatics/btt703

Measurable goals and objectives:

1. This analysis will identify differentially expressed genes with either chorioamnionitis and/or hyperoxia exposure along with pathways associated with the relevant gene expression changes.
2. Detailed analysis will further help us understanding the long term consequences of chorioamnionitis with sequential oxygen exposure such as BPD and asthma which has been shown to occur in higher frequency in neonates with these exposures at an early age.

Time Frame:

We plan to start working on the project in summer of 2025 and major part of the research work will be done before August 15, 2025. Depending on the progress, some research and writing work will be continued in fall 2025

How the project will enhance teaching and research at Lincoln University?

In future, one or more students can be involved in this research. A promising initial research finding may lead us to write proposals to seek external funding that will eventually lead to more students getting involved in undergraduate research and other interested faculty members may get involved in it too.

How the success of the project will be measured?

The research outcome will be presented in a conference, published in conference proceedings and peer reviewed journals.

How, when, where, and with whom the project's outcome will be shared?

The results of this project will be presented before faculty colleagues and students during Faculty Research symposium and a summary report of the project will be sent to the Office of Faculty Affairs.