

# Application of high dimensional flow cytometry and unsupervised analysis to define the immune cell landscape of early childhood respiratory and blood compartments

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**Manuscript Source:** <https://www.biorxiv.org/content/10.1101/2021.03.21.436363v1>

**Manuscript Authors:** Shivanthan Shanthikumar, Sarath C. Ranganathan, Richard Saffery & Melanie R. Neeland

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The sections of the research paper input text parsed in this audit.

[illegible]

Title

# Application of high dimensional flow cytometry and unsupervised analysis to define the immune cell landscape of early childhood respiratory and blood compartments

**S1 [001]**

## SUMMARY

**S1 [002]**

The cellular landscape of the paediatric respiratory system remains largely uncharacterised and as a result, the mechanisms of highly prevalent childhood respiratory diseases remain poorly understood.

The cellular landscape ...  
... of the paediatric respiratory system remains largely uncharacterised ...  
... and as a result, ...  
... the mechanisms ...  
... of highly prevalent childhood respiratory diseases remain poorly understood.

**S1 [003]**

A major limitation in defining mechanisms of disease has been the availability of tissue samples collected in early life, as well as technologies that permit deep immune analysis from limited sample volumes.

A major limitation ...  
... in defining mechanisms ...  
... of disease has been the availability ...  
... of tissue samples collected ...  
... in early life, ...  
... as well ...  
... as technologies ...  
... that permit deep immune analysis ...  
... from limited sample volumes.

**S1 [004]**

In this work, we developed new experimental methods and applied unsupervised analytical tools to profile the local (bronchoalveolar lavage) and systemic (whole blood) immune response in childhood respiratory disease.

In this work, ...  
... we developed new experimental methods ...  
... and applied unsupervised analytical tools ...  
... to profile the local ...  
... (bronchoalveolar lavage) ...  
... and systemic ...  
... (whole blood) ...  
... immune response ...  
... in childhood respiratory disease.

**S1 [005]** We quantified and comprehensively phenotyped immune cell populations across blood and lung compartments in young children (under 6 years of age), showed that inflammatory cells in the BAL express higher levels of activation and migration markers relative to their systemic counterparts, and applied new analytical tools to reveal novel tissue-resident macrophage and infiltrating monocyte populations in the paediatric lung.

We quantified ...  
... and comprehensively phenotyped immune cell populations ...  
... across blood ...  
... and lung compartments ...  
... in young children ...  
... (under 6 years ...  
... of age), ...  
... showed ...  
... that inflammatory cells ...  
... in the BAL express higher levels ...  
... of activation ...  
... and migration markers relative ...  
... to their systemic counterparts, ...  
... and applied new analytical tools ...  
... to reveal novel tissue-resident macrophage ...  
... and infiltrating monocyte populations ...  
... in the paediatric lung.

**S1 [006]** To our knowledge, this is the first description of the use of these methods for paediatric respiratory samples.

To our knowledge, ...  
... this is the first description ...  
... of the use ...  
... of these methods ...  
... for paediatric respiratory samples.

**S1 [007]** Combined with matched analysis of the systemic immune cell profile, the application of these pipelines will increase our understanding of childhood lung disease with potential to identify clinically relevant disease biomarkers.

Combined ...  
... with matched analysis ...  
... of the systemic immune cell profile, ...  
... the application ...  
... of these pipelines will increase our understanding ...  
... of childhood lung disease ...  
... with potential ...  
... to identify clinically relevant disease biomarkers.

## **S2 [008] INTRODUCTION**

**S2 [009]** A detailed understanding of the tissue-specific immune landscape in health and disease is required to improve the clinical management of many childhood diseases.

A detailed understanding ...  
... of the tissue-specific immune landscape ...  
... in health ...  
... and disease is required ...  
... to improve the clinical management ...  
... of many childhood diseases.

**S2 [010]** Aberrant inflammation is a hallmark of several childhood lung diseases, including bronchopulmonary dysplasia (Balany and Bhandari, 2015), preschool wheeze (Xepapadaki et al., 2020), asthma (Chedevergne et al., 2000), cystic fibrosis (Tirouvanziam et al., 2000), primary ciliary dyskinesia (Cockx et al., 2017), and COVID-19 (Neeland et al., 2021).

Aberrant inflammation is a hallmark ...  
... of several childhood lung diseases, ...  
... including bronchopulmonary dysplasia ...  
... (Balany ...  
... and Bhandari, 2015), ...  
... preschool wheeze ...  
... (Xepapadaki et al., 2020), ...  
... asthma ...  
... (Chedevergne et al., 2000), ...  
... cystic fibrosis ...  
... (Tirouvanziam et al., 2000), ...  
... primary ciliary dyskinesia ...  
... (Cockx et al., 2017), ...  
... and COVID-19 ...  
... (Neeland et al., 2021).

**S2 [011]** Despite this, little is known regarding the immune cell profiles and mechanisms governing inflammatory processes in the early life respiratory system.

Despite this, ...  
... little is known regarding the immune cell profiles ...  
... and mechanisms governing inflammatory processes ...  
... in the early life respiratory system.

**S2 [012]** A major limitation in defining immune cell development in the paediatric lung has been the availability of tissue samples collected in early life, as well as technologies that permit deep immune analysis from limited sample volumes.

A major limitation ...  
... in defining immune cell development ...  
... in the paediatric lung has been the availability ...  
... of tissue samples collected ...  
... in early life, ...  
... as well ...  
... as technologies ...  
... that permit deep immune analysis ...  
... from limited sample volumes.

**S2 [013]** Unlike adults, children infrequently undergo surgical procedures for evaluation of lung diseases, and as such research samples are not readily obtained.

Unlike adults, ...

... children infrequently undergo surgical procedures ...  
... for evaluation ...  
... of lung diseases, ...  
... and as ...  
... such research samples are not readily obtained.

**S2 [014]** One clinical test which can be leveraged for research purposes in children is the bronchoalveolar lavage (BAL), which samples immune cells in the lung.

One clinical test ...  
... which can be leveraged ...  
... for research purposes ...  
... in children is the bronchoalveolar lavage ...  
... (BAL), ...  
... which samples immune cells ...  
... in the lung.

**S2 [015]** Furthermore, the recent advancement of multiple single cell technologies, including single-cell RNA sequencing (sc-RNAseq), single cell DNA methylation analysis (Karemaker and Vermeulen, 2018), and single cell Assay for Transposase-Accessible Chromatin sequencing (Buenrostro et al., 2015), along with improvements in existing techniques such as flow cytometry and CyTOF, now mean that small volumes of childhood BAL fluid (collected at the time of clinically indicated procedures) can be used to profile the immune cells of the lung in highly granular detail.

Furthermore, ...  
... the recent advancement ...  
... of multiple single cell technologies, ...  
... including single-cell RNA sequencing ...  
... (sc-RNAseq), ...  
... single cell DNA methylation analysis ...  
... (Karemaker ...  
... and Vermeulen, 2018), ...  
... and single cell Assay ...  
... for Transposase-Accessible Chromatin sequencing ...  
... (Buenrostro et al., 2015), ...  
... along with improvements ...  
... in existing techniques ...  
... such as flow cytometry ...  
... and CyTOF, ...  
... now mean ...  
... that small volumes ...  
... of childhood BAL fluid ...  
... (collected ...  
... at the time ...  
... of clinically indicated procedures) ...  
... can be used ...  
... to profile the immune cells ...  
... of the lung ...  
... in highly granular detail.

## **End of Sample Audit**

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