Ann Maree Bosch Career Fellowship Report – Dr Shivanthan Shanthikumar

Alveolar Macrophages As A Therapeutic Target In Cystic Fibrosis Lung Disease

The proposed project centered on defining the role of alveolar macrophages in cystic fibrosis lung disease and identifying novel targets for anti-inflammatory therapy. The funding was to be used for a trip to a conference and collaborating laboratories in USA in 2020, and the proposed research was based on samples collected during bronchoscopy in children with CF. Unfortunately, due to the COVID-19 pandemic the trip was not possible, and the research has been delayed due being unable to safely perform bronchoscopy. That led to a pivot in the research, which is described below, and considerable progress has been made. The funding from the fellowship was still used to facilitate collaborations with sites in USA, and in particular Emory University and the University of North Carolina. While waiting to be able to complete our alveolar macrophage targeted work we conducted preliminary work as described below:

Impact of Early Life Ivacaftor: Using samples stored in a biobank we analysed samples from children with CF who had commenced treatment with ivacaftor in early life. We compared these samples, to samples from children who had not been treated with ivacaftor. What we found was that children treated with ivacaftor reduced the severity of lung disease (which was measured using CT scan) in the long term. Interestingly we found that ivacaftor did not impact markers of inflammation, and our preliminary data suggests that the majority of the impact of ivacaftor appears to be on reducing abnormal mucus in the airways. Some of these data were presented at the North American Cystic Fibrosis Conference last year and are currently being prepared for publication.
Outcome & Significance: CFTR modulators such as ivacaftor do not appear to reduce inflammation, even when commenced in early life, and synergistic anti-inflammatory therapy will still be needed.

Alveolar Macrophage Targeted Work: We have progressed our analysis of alveolar macrophages using the methods proposed in the grant application. We have analysed samples from 52 participants (in excess of the 30 proposed in the grant). We have also analysed samples that will allow analysis of the effect of CFTR modulator therapy on alveolar macrophages. We also developed a new method that allows us to simultaneously analyse macrophage subtypes and what cytokines they express, thus combining proposed experiments 1 & 2.
We have fully characterised alveolar macrophage subtypes and are finalising analysis of associated with disease severity and modulator therapy and what cytokines they express. We have identified several macrophage subtypes of interest including subtypes that only appear in children with CF and have not been found in healthy controls or older adults. These may represent a logical target for anti-inflammatory therapy.

Despite being significantly limited by the COVID-19 pandemic we have nearly completed the proposed research but have included more participants and developed novel methods. In addition, we have completed an additional experiment that reinforces the importance of this work. ***We thank the Australian Cystic Fibrosis Research Trust for their support, as without it this work would not have been possible.***

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200 word project description written for educated non-specialists

A major cause of lung disease in cystic fibrosis (CF) is excessive inflammation which causes irreversible lung damage. Currently a number of treatments are used in CF such as antibiotics and physiotherapy, however no treatments target inflammation. There are new treatments, called modulators, which address the malfunctioning ion channel which causes CF. However, not all people with CF can use these treatments. Any treatments aimed at inflammation in CF would benefit all patients, and could be used together with existing and new treatments. There are a number of different cell types that contribute to inflammation, however one that has not been investigated is the alveolar macrophage.

The Ann Maree Bosch Career Fellowship grant allowed me to collaborate with international researchers and complete research that found modulators do not improve lung inflammation and hence we still need to identify new anti-inflammatory therapy. In further research we have characterised all of the alveolar macrophage subsets in the CF lung, and found subsets that only occur in children with CF. These subsets may be a logical target of anti-inflammatory therapy. We are currently finalising our analysis to determine exactly how these alveolar macrophage subsets function and how they can be targeted with anti-inflammatory treatments.