Project Title:	To determine the role of PGD2/CRTh2 axis on non-classical monocytes in asthma		
Application Deadline:	Applications accepted all year round		
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Summary
(no more than 200 words)

Background

The Prostaglandin D2 / prostaglandin D2 receptor (also known as CRTh2) axis plays an important role in allergic and Type 2 (T2)-mediated moderate to severe asthma [1-3]. In line with this, CRTh2 is expressed on effector cells of T2 inflammation such as ILC2s, Eosinophils, Basophils and Th-2 /Tc-2 cells. In these cells activation of CRTh2 initiates shape change [4], chemotaxis and enhances ILC2 and Th-2 type-2 cytokine secretion [5-7]. Fevipiprant (an oral antagonist of CRTh2 with efficacy in asthma) has been suggested to block the action of these effector cells. Nagata et al. [8] suggested that a monocyte subpopulation expressed CRTh2 but the functional role of CRTh2 on these cells has not been explored. Monocytes are heterogenous [9] antigen presenting cells whose role in asthma is not clearly understood. Fevipiprant may thus act early during T cell priming to block the establishment of memory Th-2 responses by antigen presenting cells, which could lead to greater mechanistic understanding of Fevipiprant and the role of CRTH2.

Classical monocytes express CRTh2 mRNA (encoded by the PTGDR2 gene) but not cell surface protein [5], whereas non-classical monocytes (which derive from classical monocytes) express both mRNA and protein [10]. CRTh2 expression on dendritic cell subsets in blood is also unclear. Of note, single cells transcriptomics of human blood dendritic cells and monocytes has recently revealed a CD141- CD1c- dendritic cell population, transcriptionally very similar to non-classical monocytes, that may be enriched for CRTh2 transcripts [9].

We have set up robust protocols that have confirmed non-classical monocyte expression of cell surface CRTh2 and allow simultaneous evaluation of dendritic cells. We wish to explore monocyte frequency in blood and lung tissue, focus on the effect of CRTh2 activation in non-classical monocytes, at the transcriptional and functional level, in health and disease (asthma and COPD). Techniques will include Flow Cytometry, qPCR, Immunohistochemistry, molecular biology and cell culture.

Hypothesis

PGD2 stimulation of non-classical monocytes is active in asthma and promotes T2-dependent memory/effector T cell responses

References

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