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Ivacaftor modifies cystic fibrosis neutrophil phenotype in subjects with R117H residual function CFTR mutations

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To the Editor:

Cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy (ivacaftor, lumacaftor, tezacaftor) treats the basic defect in cystic fibrosis (CF) by increasing CFTR function and improving lung function and quality of life. CF lung disease is characterised by chronic bacterial colonisation, inflammation and excessive neutrophilia [1]. The confirmation of CFTR expression on neutrophils [2] led to speculation that immune cell dysfunction may be implicated in CF lung inflammation. Neutrophils from CF patients with severe CFTR mutations (*e.g.* F508del and G551D) have prolonged neutrophil survival [3] and decreased phagocytosis and degranulation. The residual function R117H mutation causes a 25% decrease in channel conductance [4], and when present in combination with a second severe mutation (*e.g.* F508del) results in CFTR function that lies somewhere between heathy controls and typical CF. CF patients with residual function develop disease at a later stage and ivacaftor is now licensed for the treatment of the R117H mutation having been demonstrated to be effective in clinical trials [5]. Treatment of people with G551D mutations with ivacaftor also has significant mutation specific effects on myeloid cells [6]. Therefore, we assessed the effects of CFTR modulator therapy on neutrophil phenotype and function in this group.