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Title: Mucosal explant induced migration of T-cells from severe asthmatics is inhibited by CCR4 antagonism

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Body: Background: Th2 cells that express chemokine receptor 4 (CCR4) are key to inflammation in asthma. Work in mild asthma patients suggests that CCR4 plays a role in Th2 migration into the lung, making CCR4 a possible therapeutic target. However, little evidence is known on the role of CCR4 on Th2 migration in severe asthma patients on high dose corticosteroids. Aim: To investigate if chemokines released by mucosal explants, from asthma patients on high dose inhaled corticosteroids, drive Th2 migration and if such a response is CCR4 dependent. Methods: Bronchial explants, from 11 severe (SA) and 9 steroid naïve (SNA) asthma patients, were cultured in media +/- house dust mite extract. The supernatants were used as chemoattractants in migration assays with patient-matched peripheral T-cells. The effects of three CCR4 antagonists, GSK494652A, GSK2239633A and GSK2192991A, on T-cell migration were examined. Results: Bronchial explant conditioned media from SNA induced higher T-cell migration than that from SA ($p=0.03$). However, house dust mite extract did not enhance chemotaxis in either SNA ($p=0.9$) or SA ($p=0.6$). Inhibition of CCR4 reduced T-cell migration in response to unstimulated explant conditioned media (Table 1).

Table 1:Effects of CCR4 antagonists on T-cell migration.

	Chemotaxis Index			
	Control	GSK494652A	GSK2239633A	GSK2192991A
SNA Median (range)	2.7 (0.8-17.2)	1.7* (0.6-10.1)	1.7* (0.6-11.2)	1.9* (0.8-7.8)
SA Mean (sem)	2.0 (0.3)	2.2 (0.4)	1.6*(0.2)	1.4*(0.2)

Control V antagonist:*$p<0.05$

Conclusions: Targeting CCR4 may prove to be effective in reducing Th2 recruitment into the lung and the subsequent inflammatory response in asthma patients who are on high dose inhaled corticosteroid

treatment.