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Title: p38 MAPK inhibitors in COPD

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Body: p38 MAPK signalling upregulates inflammation and is known to be increased in COPD. This study investigated whether p38 inhibitors PF75 and PF32 suppressed release of inflammatory cytokines from macrophage-lineage cells. Peripheral blood mononuclear cells (PBMC) and monocyte-derived macrophages (MDM) were isolated from non-smokers (NS), smokers (S) and COPD patients. Cells were pre-treated with either p38 inhibitor or dexamethasone (DEX) prior to stimulation with LPS. Cell media was harvested at 24h and cytokine release (IL-6, CXCL8, IL-10 and TNF) measured by ELISA. Both p38 inhibitors and DEX suppressed cytokine release in a concentration-dependent manner in PBMC and MDM. There were no differences between subject groups.

EC50 values (nM) for DEX, PF75 and PF32 on cytokine release

	PBMC	PBMC	PBMC	MDM	MDM	MDM
	NS	S	COPD	NS	S	COPD
DEX	n=10	n=11	n=13	n=8	n=11	n=12
TNF	358±273	46.8±8.23	53.2±17.6	13.6±6.98	16.9±10.2	62.3±3.01
IL-6	33.5±13.3	24.9±10.5	43.4±14.1	27±11.2	3.14±3	21.9±11.7
CXCL8	32.4±16.8	16.0±5.33	22.2±9.63	21.9±11.7	3.45±1.88	19.3±8.27
IL-10	25.8±10.1	240±158	29.5±12.8	16.1±7.43	23.8±10.4	126±101
PF75	n=6	n=10	n=8	n=6	n=9	n=7
TNF	9.23±2.87	12.4±4.12	10.6±4.14	5.47±2.74	3.31±1.48	3.4±0.99
IL-6	21.4±9.62	15.1±7.84	43.1±20.3	4.82±2.74	1.03±0.96	1.91±1.5
CXCL8	30.8±15.5	1.3±1.06	38.4±34.3	5.96±3.84	1.71±1.41	0.07±0.03
IL-10	4.72±4.59	23.4±17.8	514±327	34.6±30	3.98±3.83	20.8±12.9
PF32	n=8	n=9	n=7	n=6	n=7	n=6

TNF	1.04±0.38	1.96±0.57	1.57±0.64	0.76±0.59	0.50±0.34	2.31±0.85
IL-6	0.65±0.53	0.10±0.02	10.2±8.57	4.97±4.51	6.22±6.00	234±232
CXCL8	3.37±1.83	1.72±1.05	0.99±0.51	2.48±2.4	3.7±3.02	1.66±1.01
IL-10	1.49±0.68	229±228	2.01±0.87	4.94±4.86	1.93±1.41	0.65±0.46

mean ± SEM; n= number of subjects

p38 inhibitors suppress release of inflammatory cytokines and may have a therapeutic role in COPD.