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Anti-inflammatory effects of LASSBio-998, a new drug candidate designed to be a p38 MAPK inhibitor, in an experimental model of acute lung inflammation

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Abstract:
We investigated the effects of LASSBio-998 (L-998), a compound designed to be a p38 MAPK (mitogen-activated protein kinase) inhibitor, on lipopolysaccharide (LPS)-induced acute lung inflammation *in vivo*. BALB/c mice were challenged with aerosolized LPS inhalation (0.5 mg/ml) 4 h after oral administration of L-998. Three hours after LPS inhalation, bronchoalveolar lavage fluid was obtained to measure the levels of the proinflammatory cytokines TNF-α (tumor necrosis factor-α) and IL-1 (interleukin-1) and the chemokines MCP-1 (monocyte chemoattractant protein-1) and KC (keratinocyte chemoattractant). In addition, neutrophil infiltration and p38 MAPK phosphorylation was measured. L-998 inhibited LPS-induced production of TNF-α and IL-1β, and did not alter KC and MCP-1 levels. Furthermore, L-998 also significantly decreased neutrophil accumulation in lung tissues. As expected, L-998 diminished p38 MAPK phosphorylation and reduced acute lung inflammation. Inhibition of p38 MAPK phosphorylation by L-998 was also demonstrated in LPS-challenged murine C57BL/6 peritoneal macrophages *in vitro*, with concentration-dependent effects. L-998 suppressed LPS-induced lung inflammation, most likely by inhibition of the cytokine-p38 MAPK pathway, and we postulate that L-998 could be a clinically relevant anti-inflammatory drug candidate.

Key words:
LASSBio-998, TNF-α, lung inflammation, p38 mitogen-activated protein kinase, anti-inflammatory drug candidate

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