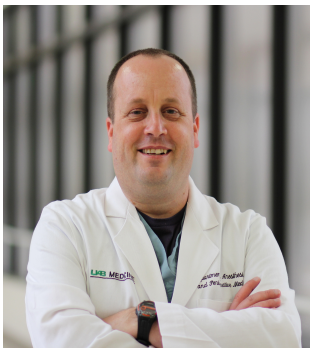

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Title: "The Role of PDE4 in IL-8-dependent Inhibition of cAMP-stimulated Alveolar Fluid Clearance"

Synopsis: Acute respiratory distress syndrome (ARDS) is a syndrome manifested by rapid onset of respiratory failure associated with significant mortality due to influx of protein-rich fluid into lung spaces. The two most common reasons for ARDS are sepsis and hemorrhagic shock. In normal patients, the beta2-adrenergic receptor (β_2AR) agonists activate cyclic-adenosine monophosphate (cAMP) to stimulate alveolar fluid clearance (AFC) and remove fluid from the airspace of the lungs. However, most of patients with ARDS have impaired AFC and two large clinical trials have failed to show a survival benefit in patients treated with β_2AR agonists. Interleukin 8 (IL-8) is one of the biomarkers that are elevated in pulmonary edema fluid from ARDS patients. Levels of IL-8 comparable to those measured in the pulmonary edema fluid of ARDS patients have been shown to inhibit β_2AR-stimulated, cAMP-mediated AFC. Hence, this may be one of the mechanisms explaining why the treatment with β_2AR agonists has failed in patients with ARDS. Furthermore, this mechanism is phosphoinositol-3 kinase (PI3K)-dependent. Not only has PI3K been shown to decrease β_2AR activity via phosphorylation of the inactive receptor leading to decreased cAMP activity, it also activates phosphodiesterase (PDE) 4 that actively decreases cAMP within the cell. As PDE4 inhibitors are already in clinical use in pulmonary diseases such as asthma and COPD, demonstrating these inhibitors may reverse the inhibitory effect of IL-8 on AFC in ARDS patients and may lead to new therapeutic approaches for these patients.
We demonstrate that IL-8 leads to heterologous desensitization and downregulation of the β_2AR making it unavailable for activation by agonists. However, treatment with rolipram (a PDE4 inhibitor), reverses these effects and restores β_2AR-stimulated, cAMP-mediated AFC both *in vitro* and *in vivo*.