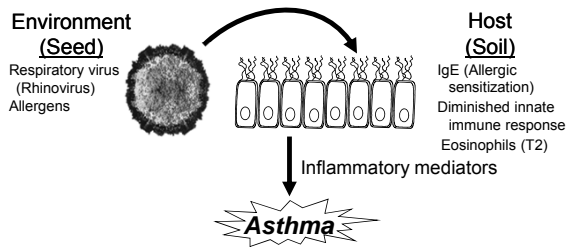


Identifying Biologic Targets to Attenuate or Eliminate Asthma Exacerbations

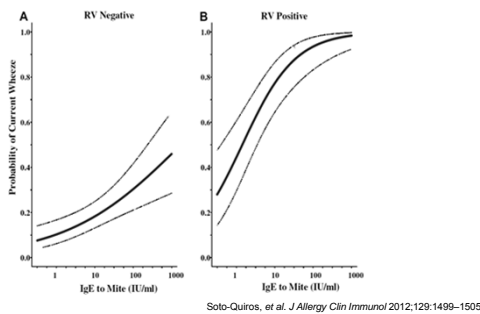
Asthma exacerbations are a major cause of disease morbidity and costs. For both children and adults, viral respiratory infections are the major cause of these exacerbations. The mechanisms underlying these episodes are complex and involve multiple cells and factors. With the use of biologics to treat more severe asthma and exacerbation-prone patients, greater insight has been gained into the targets, and consequently, the mechanisms by which respiratory viruses, particularly the common cold virus – rhinovirus, lead to exacerbations. The following discussion on biologic targets for exacerbations will focus on major risk factors in this process: IgE, allergic sensitization, deficiencies in innate immunity, particularly interferon generation, and the multiple cells and pathways involved. The unfolding of this new information has not only provided greater insight to this major cause of asthma morbidity, and its loss of control, but also is identifying new targets whose targeted control promises to lead to improved outcomes and the attenuation or prevention of exacerbations.

What are key biologic targets in asthma exacerbations?

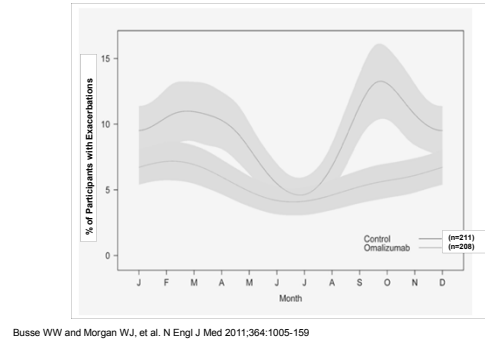


What role does IgE play in asthma exacerbations?

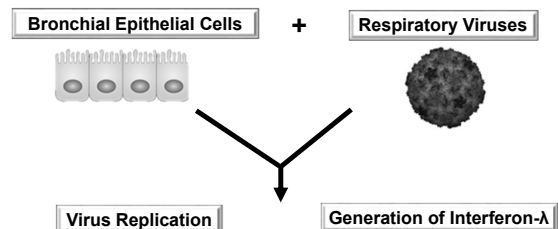
What is the effect of IgE antibody to dust mite allergen and risk for wheezing among asthmatic children infected with rhinovirus?



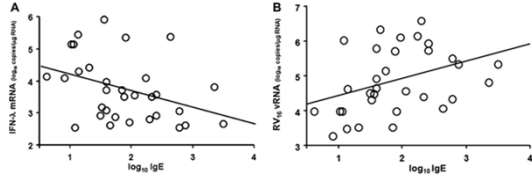
What is the effect of omalizumab on asthma exacerbations on a seasonal basis?



What role do innate immune responses play in asthma exacerbations?

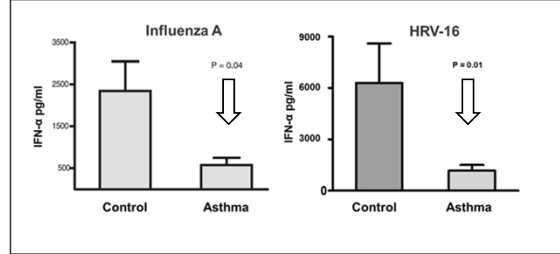


Total Serum IgE Levels



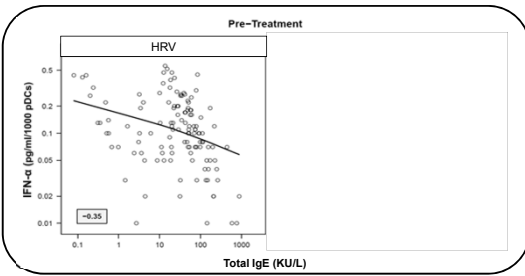
Baralado et al. J Allergy Clin Immunol 2012; 130:1307-1314.

Is dendritic cell (pDC) generation of IFN-α antiviral impaired in patients with allergic asthma?

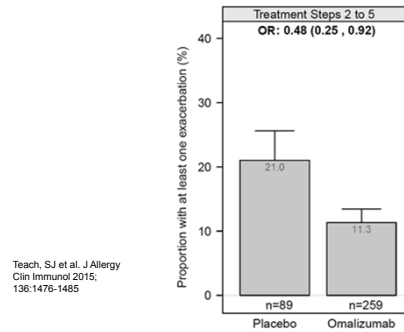


J. Immunol., 2010, 184 (11), 5999-06.

What is the relationship between IgE and virus-induced IFN-α generation?

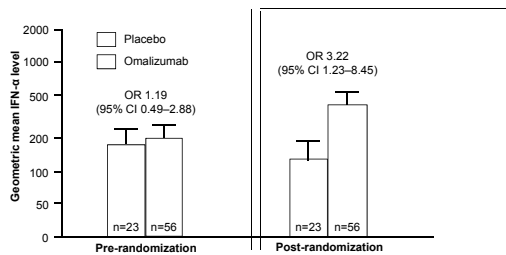


What effect does omalizumab have on seasonal exacerbations of asthma in PROSE?



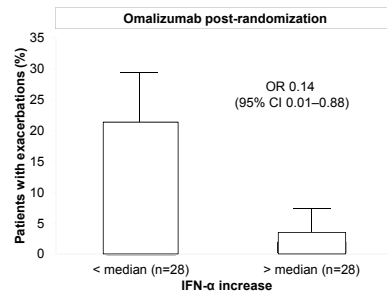
Teach, SJ et al. J Allergy Clin Immunol 2015; 136:1476-1485

What effect does omalizumab treatment have on *in vitro* generation of IFN-α from isolated PBMC incubated with RV?



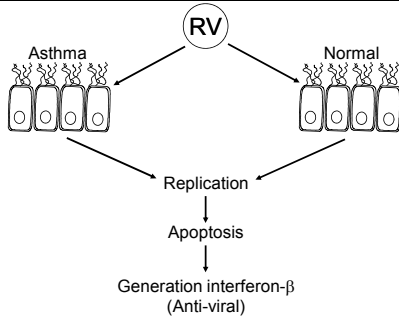
Teach, SJ et al. J Allergy Clin Immunol 2015;136:1476-1485

What is the effect of restoring IFN-α generation to asthma exacerbations?



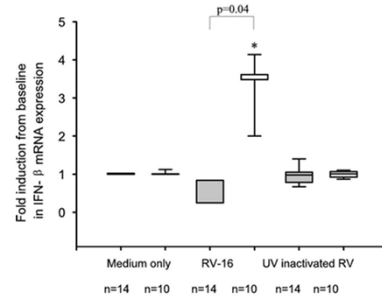
Teach, SJ et al. J Allergy Clin Immunol 2015;136:1476-1485

Is there a difference in bronchial epithelial cell generation of interferon between normal and asthma?



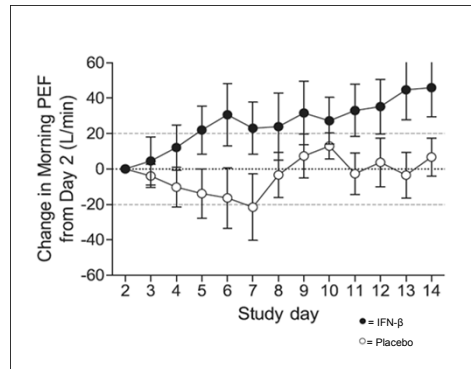
Wark et al. J Exp Med 2005; 201:937-947.

Impaired IFN-β production in asthma

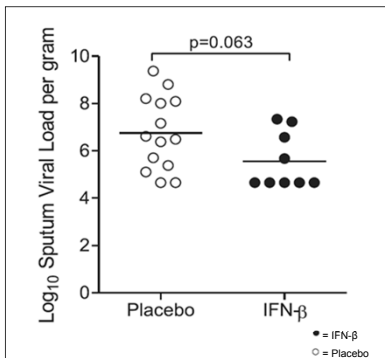


Wark et al. J Exp Med 2005; 201:937-947.

Djukanović R, et al. The effect of inhaled IFN-β on worsening of asthma symptoms caused by viral infections. Am J Respir Crit Care Med 2014;190:145-154.

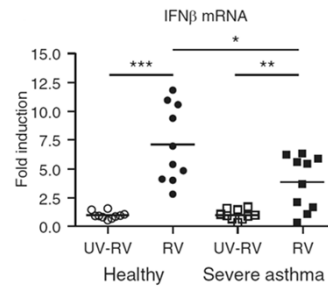


Djukanović et al. Am J Respir Crit Care Med 2014;190:145-154.



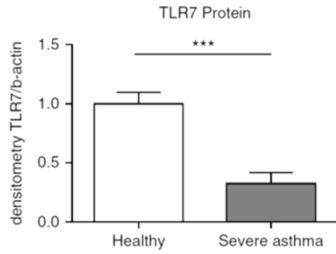
Djukanović et al. Am J Respir Crit Care Med 2014;190:145-154.

What is the alveolar macrophage expression of interferon-β to RV in severe asthma?



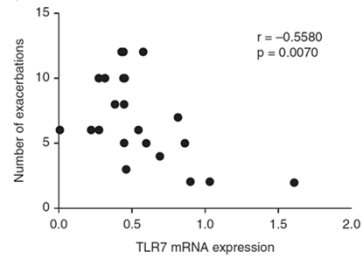
Rupani H., et al. Am J Respir Crit Care Med 2016;194:28-37.

What is the comparative of TLR7 protein generation by AM to RV in severe asthma?



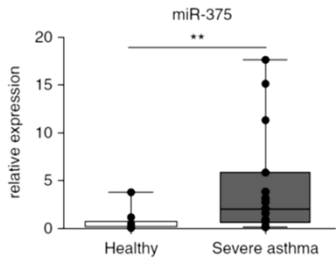
Rupani H., et al. Am J Respir Crit Care Med 2016;194:26-37.

Is there a relationship between TLR7 expression by AM and frequency of exacerbation in severe asthma?



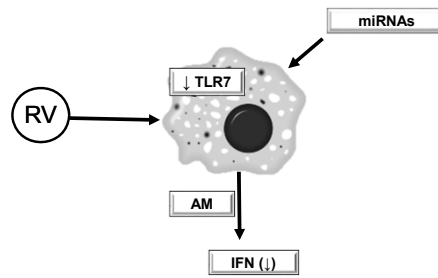
Rupani H., et al. Am J Respir Crit Care Med 2016;194:26-37.

What is the comparative AM expression of miRNAs in healthy and severe asthma subjects?

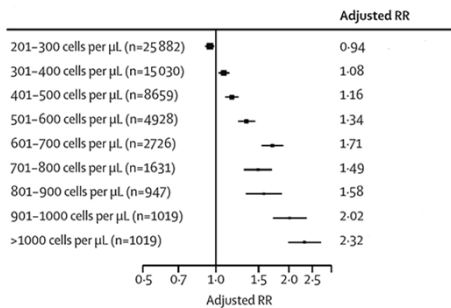


Rupani H., et al. Am J Respir Crit Care Med 2016;194:26-37.

Alteration of alveolar macrophage generation of interferons



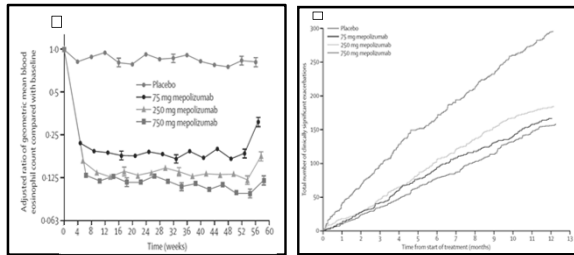
What is the relationship of blood eosinophils to severe asthma exacerbations?



Price DB, et al. Lancet Respir Med 2015;3:849-58.

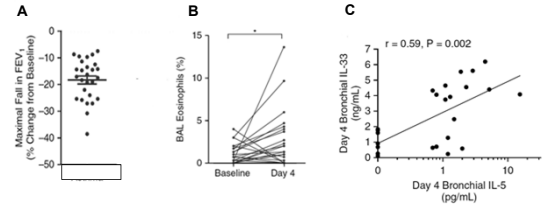
Pavord ID, et al. Mepolizumab (anti-IL-5) for severe eosinophilic asthma (DREAM). Lancet 2012;380:651-59.

- Evaluated mepolizumab (75, 250 and 750 mg) vs. placebo
 - 621 adult patients on high doses of ICS and with one or more of the following
 - 2 or more exacerbations in previous year
 - Sputum eosinophils $\geq 3\%$
 - FeNO ≥ 50 ppb
 - Blood eosinophils ≥ 300 /microliter
- } Increased susceptibility factors for exacerbations



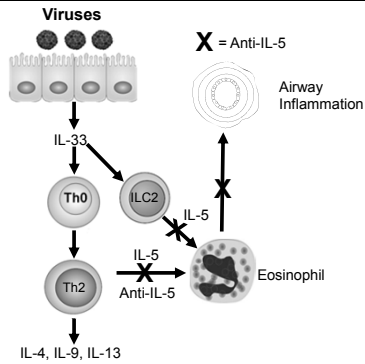
Pavord ID, et al. Lancet 2012;380:651-659.

What is the effect of a RV infection on asthma, eosinophils, IL-33 and IL-5?



Jackson DJ, et al. Am J Respir Crit Care Med 2014;190:1373-1382

How may anti-IL-5 affect virus-induced asthma exacerbations?



What are key biologic targets that may promote asthma exacerbations?

