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**Title:** Precision cut lung slices: A novel method for examining mechanisms underlying respiratory diseases

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**Body:** Bacterial infections and smoking have been linked to exacerbations of many respiratory diseases. To this end, responses to toll-like receptor (TLR) agonists and bacterial pathogens were studied in precision cut lung slices (PCLS) from room air and smoke-exposed mice. Ex vivo cultured PCLS were either left untreated or stimulated with toll-like receptor agonists, lipopolysaccharide (LPS), or Pam3CSK. An additional set of PCLS were challenged with either live or heat-killed Haemophilus influenzae, or Streptococcus pneumoniae. RNA was isolated and microarray analysis performed. Principal component analysis showed that live S. pneumoniae stimulation of PCLS led to a distinct response and a greater number of differentially expressed genes (DEGs) when compared to the responses elicited by the two TLR agonists or H. influenzae. Unsupervised hierarchical clustering analysis was performed on 1846 DEGs identified 24 hours post-stimulation in room air exposed PCLS, and two distinct clusters were present, confirming the principal component analysis. Of the 1354 genes identified following live S. pneumoniae challenge of room air PCLS, several signaling cascades were identified following ingenuity pathways analysis (IPA); these included the IL-1 and IL-10 signaling cascades. In the context of cigarette smoke exposure, IPA analysis captured pathways involved in airway pathology in COPD. These data highlight the strength of this technique for evaluating pathways that may be linked to disease (or exacerbation) susceptibility. Finally, mechanisms that have been implicated in COPD pathogenesis are captured in this model, and therefore increase the validity of this method to test interventions.