

**LTRC Concept Sheet # 07-01-0001**

**Neurotrophins in the Lung**

**ABSTRACT**

An exciting, new investigative theme in airway physiology and pathophysiology is neurotrophins (NTs): growth factors including brain-derived neurotrophic factor (BDNF) and neurotrophins 3 (NT3) and 4 (NT4), known for their diverse roles in the nervous system. Preliminary reports indicate that NTs and their receptors are expressed by different lung components in humans including epithelial cells, nerves and even airway smooth muscle (ASM). Analysis of sputum and bronchoalveolar lavage samples shows increased NT expression in diseases such as asthma, allergy, and even lung cancer. However, the specific role(s) of NTs in the airway is(are) still under investigation. While NTs may be derived from several sources, our published and preliminary data suggest that ASM is a target of NTs, and that NTs contribute not only to ASM contractility under normal circumstances, but also to increased contractility with airway inflammation. Furthermore, other data from our group suggests that airway innervation modulates NT signaling in ASM itself (e.g. substance P enhances BDNF signaling). The long term goal of the proposed studies is to understand the role of NTs in ASM physiology and pathophysiology. To this end, it is important to first establish the relative expression and distribution of NTs and their receptors in human ASM itself under both “normal” conditions and in diseases known to involve ASM, i.e. COPD. Corollary studies should establish whether airway innervation (relevant to NT signaling; e.g. SP or neurokinin receptor expression) is altered in disease states. Furthermore, the signal transduction cascades activated by NTs overlap considerably with mechanisms activated by inflammatory cytokines (e.g. TNF $\alpha$ ) and in diseases such as IPF and COPD. Accordingly, mRNA and protein analysis of tissue extracts would provide key information on which signaling pathways may be relevant in the lung. Thus, tissue blocks and aliquots obtained via the LTRC (“controls” vs. COPD patients) will be processed for immunocytochemistry (with confocal imaging), molecular biology (mRNA, RT-PCR) and biochemistry (protein expression).