

**Science Advance in Cancer**  
*Congressional Hearings Feb. 2006*

**COBRE Center for Cancer Research Development/Grant Number P20 RR017695**

**Title: Molecular & Cellular Factors in Cancer of the Throat**

**Background:** Acid reflux disease (commonly called heartburn) affects more than one in ten adults over 40 years of age and one in four adults over 60. Approximately 10% of the patients with this ailment develop precancerous changes in the lining of their throat (Barrett's esophagus), the result of repeated damage caused by stomach acid. Without treatment, these patients have a 30-125-fold increased risk for developing throat cancer. At present, the mechanisms whereby acid reflux accelerates the progression from Barrett's esophagus to throat cancer are poorly understood.

**Advance:** Dr. Weibiao Cao and his co-workers, aided by support from the COBRE for Cancer Research Development (NCRR P20 RR17695) have identified a protein called NADPH oxidase that appears to play a central role in the damage caused by acid reflux. This enzyme produces hydrogen peroxide, which is known to cause damage to the DNA of cells that line the throat. When cancer cells appear, the high levels of hydrogen peroxide increases their growth and decreases their death rate. Dr. Cao has shown that Levels of a subunit of NADPH oxidase (NOX5) are significantly higher in throat cancer cells than in normal patients or patients with Barrett's esophagus. To mimic the effects of acid reflux, cultured cells were exposed to brief pulses of dilute acid, a treatment that significantly increased the levels of NOX5 and production of hydrogen peroxide. Suppression of NOX5 expression in cancer cells blocked acid induced production of hydrogen peroxide. In addition, acid treatment caused an increase in calcium concentration inside of the cells and activated a protein that regulates the expression of NOX5, the end result being increased NOX5 levels and elevated production of hydrogen peroxide.

**Implication:** These results suggest that complete acid suppression using high doses of acid inhibitors in Barrett's esophagus patients with or without symptoms may be important for prevention of the progression from Barrett's esophagus to throat cancer. In addition, scientists may have a number of potentially useful targets to prevent and treat this lethal tumor because of the findings that NOX5 mediated overproduction of hydrogen peroxide is responsible for increased growth and decreased death of cancer cells.

**Xiaoying Fu, David G. Beer, Jose Behar, Jack Wands, David Lambeth, Weibiao Cao.** cAMP response element binding protein (CREB) mediates acid-induced NADPH oxidase NOX5-S expression in Barrett's esophageal adenocarcinoma cells. *Journal of Biological Chemistry* 2006 (tentatively accepted).