Long-Term Treatment With NAC in Cystic Fibrosis Patients

A Phase II Randomized Placebo-Controlled Trial

Stanford University
Carol Conrad, MD and Rabin Tirouvanziam, PhD
The Role of Oxidants and Anti-Oxidants in Biological Systems

- DNA transcription and translation
- Protein function and release from intracellular compartments
- Protein trafficking
- Cell cycling/cell death
- Scavenging Reactive Oxygen Species
Anti-Oxidants and Oxidants are Kept In Balance: Glutathione is the Major Anti-Oxidant for the Body
The Roles of Oxidants and Anti-Oxidants in Biological Systems

- Nucleus
- Protein Synthesis
- Mitochondria

Balance: Healthy – Damage Repair
Imbalance: Poor Damage Repair – Cell Death/Inflammation/Infection
Anti-Oxidants Counteract Inflammation

- When there are not enough antioxidants to protect the cells, reactive oxygen molecules attack healthy cells and break down tissue.
- The 'Master Antioxidant' of the body that recharges all cells and organs is glutathione (GSH).
- GSH is probably the most important cellular defense that allows the body to prevent and fight infections and disease.
Glutathione Deficiency in CF

- Normal concentration of GSH in human lung lining fluid is 140x that of plasma.
- GSH in CF Epithelial Lining Fluid (ELF) is low.¹
  - A decrease in GSH content in ELF increases susceptibility of lung to chronic inflammation in CF.
- Blood levels of GSH are low in CF.¹,²
- Blood neutrophils are low in GSH in CF.²

²Tirouvanziam, R.M. et al. PNAS, 2006, 103
CF Airways Are Inflamed

• The body's immune response relies on various white blood cells (WBCs) and natural barriers to block any attack any foreign invader.
• CF lung disease is characterized by massive numbers of neutrophils (a type of WBC) attracted to the lungs all the time.
• Too many uncontrolled neutrophils cause damage and produce oxidative molecules called reactive oxygen species (ROS). ROS are highly unstable and cause damage.
• CF patients have low body stores of GSH, a major antioxidant naturally produced in the body.
How Redox Stress Relates to CF Airway Inflammation

Oxidation Stress → Hydrogen Peroxide

- GSH → Glutathione Peroxidase → GSSG

- MPO

- Chlorine Bleach
  - Activate/Inactivate Proteases
  - Lipid Oxidation
  - Oxygen Free Radicals
Why Choose NAC?

• Taken orally, NAC is absorbed into the intestinal cells, metabolized into cysteine, then the cells make GSH and secrete it into the blood.

• The liver cells use cysteine to make glutathione (GSH) which is probably the major source of GSH production. GSH is carried by the liver’s major protein, albumin, to tissues and released into the cells.

• Tissues also can take in albumin and break it down into cysteine, and make their own GSH.
NAC - Plop-plop, fizz-fizz, Oh, what a relief it is!

A Pleasant Alkalizing Drink
Made with Alka-Seltzer—the modern Effervescent Tablet

Thousands have found that ALKA - SELTZER brings prompt and pleasant relief from Acid Indigestion, Headache, Colds, Fatigue, Morning After, Muscular Rheumatic, Sciatic Pains and other ailments caused by excess acid.

It is called Alka-Seltzer because it makes a sparkling alkaline drink. As it contains an analgesic (Acetyl-Salicylate) it first relieves the pain of everyday ailments and then by restoring the alkaline balance corrects the cause when due to excess acid. Alka-Seltzer is not a laxative.

Alka-Seltzer

30 Minutes Later → FEELING FINE
Phase II “Proof of Concept” Trial

• The design of this study based on results of Phase I Stanford trial – NAC appeared to have anti-inflammatory effects in the sputum of CF patients.

• Hypothesis: GSH replenishment to blood neutrophils will allow for a decrease in neutrophil inflammation in the sputum of CF subjects as determined by sputum elastase activity.
Phase II Trial: Effects of NAC on Redox Changes, Lung Inflammation and Lung Function

• **Treatment:** Oral NAC fizzy tablets, 1 tab (900 mg) or placebo, orally 3x/day.
  • Primary efficacy measures: sputum elastase activity
  • Secondary efficacy measures: Lung function - FEV$_1$(% pred.)

• **Schedule of Visits:** Sputum, blood, PFT’s, and Quality of Life questionnaire on Day 0 and Week 6, Week 12, and Week 24.
Phase II Trial: Effects of NAC on Redox Changes, Lung Inflammation and Lung Function

- **Staged enrollment:** Stanford first cohort
  - In-depth studies to assess if any potential for pulmonary hypertension
  - 16 subjects completed study
    - No AE’s related to NAC
    - No PH (detected by ECHO, DLCO, no free NAC in plasma, no S-nitrosylated NAC detected in plasma)

- **Other sites initiated after safety confirmation**
  - 11 sites/80 subjects planned/70 enrolled
  - Smaller panel PH studies
Primary Objective

• Eval effect of NAC on Neutrophil Elastase in sputum (destructive enzyme produced by white blood cells)

Secondary Objectives

• Eval effect of NAC on lung function
• Eval effect of NAC on number of pulmonary and sinus exacerbations, antibiotic use
• Eval effect of NAC on inflammation in the lungs (neutrophil count)
• Eval effect of NAC on weight
• Eval effect of NAC on QOL
Safety Objectives

- Safety and tolerability
- Eval if NAC causes pulmonary hypertension if used routinely in high doses
Inclusion Criteria

• 7 years of age and older
  • Able to tolerate sputum induction
  • Perform reproducible spirometry
• Stable mild to moderate lung disease
• No use of acute antibiotics in prev. 4 weeks
• Must stop use of anti-oxidants in any form at least 6 weeks prior to and for the duration of the study
  • Usual doses of Vit E and C allowed
Exclusion Criteria

- NSAID (ibuprofen, etc) use in previous 1 week
  - To assure sputum neutrophil count and elastase are at ‘baseline’
- Initiation of chronic dosing with azithro, ibuprofen, TOBI, IH Aztreonam or Colistin within previous 6 weeks
- Liver disease
- Active ABPA in previous 6 months
- Acetaminophen use in previous 3 days
Enrollment

91 Total Assessed for Eligibility

85 Screened for Eligibility

6 Not Eligible
15 Failed screening

Stanford Cohort
N = 16
Staggered Enrollment/Early
Cohort to Assess PH:
Other sites began enrollment after
DSMB review of PH data in first 8
subjects to complete Week 8 visit

8 NAC, 8 Placebo

Follow up:
Week 12: 16
Week 24: 16

0 withdrawals

All Other Sites
N = 54

28 NAC

Follow up:
Week 12: 33
Week 24: 30

6 Withdrawals
5 Subject Decision
1 Due to AE not drug
related

26 Placebo

Follow up:
Week 12: 32
Week 24: 32

2 Withdrawals
1 Subject Decision
1 Lost to Follow-up

ITT Population:
36 NAC
34 Placebo

PP Population:
18 NAC
23 Placebo

Stanford Cohort
N = 16
Staggered Enrollment/Early
Cohort to Assess PH:
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ITT Population:
36 NAC
34 Placebo

PP Population:
18 NAC
23 Placebo
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>NAC (N=36)</th>
<th>Placebo (N=34)</th>
<th>Total (N=70)</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>N (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Female</td>
<td>16 (44)</td>
<td>19 (56)</td>
<td>35 (50)</td>
<td>0.34</td>
</tr>
<tr>
<td>DF508</td>
<td>18 (50)</td>
<td>16 (47)</td>
<td>34 (49)</td>
<td>0.46</td>
</tr>
<tr>
<td>7 - &lt; 18 yrs</td>
<td>9 (25)</td>
<td>10 (29)</td>
<td>19 (27)</td>
<td>0.68</td>
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<tr>
<td>Azithro</td>
<td>23 (64)</td>
<td>24 (71)</td>
<td>47 (67)</td>
<td>0.55</td>
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<tr>
<td>AZLI or TOBI</td>
<td>23 (64)</td>
<td>17 (50)</td>
<td>40 (57)</td>
<td>0.24</td>
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</table>
# Baseline Pulmonary Function

<table>
<thead>
<tr>
<th></th>
<th>NAC (N=36)</th>
<th>Placebo (N=34)</th>
<th>Total (N=70)</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>FEV&lt;sub&gt;1&lt;/sub&gt; (% pred)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40% - &lt;60%</td>
<td>15 (42%)</td>
<td>13 (38%)</td>
<td>28 (40%)</td>
<td>0.77</td>
</tr>
<tr>
<td>60% - 85%</td>
<td>21 (58%)</td>
<td>21 (62%)</td>
<td>42 (60%)</td>
<td></td>
</tr>
<tr>
<td>All x (SD)</td>
<td>62.9 (13.4)</td>
<td>63.8 (13.2)</td>
<td></td>
<td>0.44</td>
</tr>
</tbody>
</table>
## Summary Results - Primary and Secondary Analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment Effect (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (% pred)</td>
<td>4.4 (0.83, 7.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>0.15 (0.03, 0.28)</td>
<td>0.02</td>
</tr>
<tr>
<td>Sputum Neutr. Elastase (Log$_{10}$)</td>
<td>0.21 (-0.07, 0.48)</td>
<td>0.14</td>
</tr>
<tr>
<td>Sputum Neutrophil Count (Log$_{10}$)</td>
<td>2.6 (-12.1, 17.3)</td>
<td>0.73</td>
</tr>
<tr>
<td>Sputum IL-8 (Log10)</td>
<td>0.19 (-0.03, 0.42)</td>
<td>0.09</td>
</tr>
<tr>
<td>Plasma IL-8 (Log10)</td>
<td>-0.1 (-0.33, 0.14)</td>
<td>0.42</td>
</tr>
<tr>
<td>GSH in whole blood</td>
<td>64.2 (-177.6, 305.9)</td>
<td>0.60</td>
</tr>
<tr>
<td>Incidence of Pulm Exacerbation</td>
<td>-0.08 (-0.30, 0.14)</td>
<td>0.48</td>
</tr>
<tr>
<td>New use of antibiotics</td>
<td>0.08 (-0.14, 0.29)</td>
<td>0.50</td>
</tr>
<tr>
<td>CFQ-R Respiratory Domain</td>
<td>-0.34 (-6.3, 5.67)</td>
<td>0.91</td>
</tr>
<tr>
<td>CFRSD number of resp sx</td>
<td>-0.15 (-1.1, 0.8)</td>
<td>0.75</td>
</tr>
</tbody>
</table>
Change in \( \text{FEV}_1 \) (Absolute volume)

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>Week 12</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relative % Δ \( \text{FEV}_1 \) (L)
Effect of Inhaled Antibiotics on FEV$_1$

![Graph showing the effect of inhaled antibiotics on FEV$_1$. The graph compares NAC, Abx, NAC, No Abx, Placebo, Abx, and Placebo, No Abx. The x-axis represents screening, week 12, and week 24, while the y-axis represents the relative change in FEV$_1$. The graph indicates a decrease in FEV$_1$ over time for all groups, with NAC, Abx showing the least decrease compared to Placebo, No Abx.](Image)
Neutrophil Elastase

![Graph showing the change in log10 HNE (mL/mL) from Screening to Week 24 for NAC and Placebo groups. The graph shows a decrease in HNE levels for both groups, with NAC showing a more significant reduction compared to Placebo.](image-url)
Time to Pulmonary Exacerbation

![Graph showing the proportion event-free over weeks since randomization for NAC and Placebo groups. The NAC group shows a higher proportion event-free compared to the Placebo group across all weeks.]
## Exacerbations and Related Events

<table>
<thead>
<tr>
<th>Event</th>
<th>NAC (N = 36)</th>
<th>Placebo (N = 34)</th>
<th>Difference (95% CI)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Pulmonary Exacerbation</td>
<td>15 (42%)</td>
<td>17 (50%)</td>
<td>-8% (-30%, 14%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Sinus Exacerbation</td>
<td>10 (28%)</td>
<td>6 (18%)</td>
<td>10% (-10%, 29%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>12 (33%)</td>
<td>12 (35%)</td>
<td>-2% (-23%, 19%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>30 (83%)</td>
<td>28 (82%)</td>
<td>-2% (-23%, 19%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Oral Antibiotics</td>
<td>22 (61%)</td>
<td>19 (56%)</td>
<td>5% (-17%, 27%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Inhaled Antibiotics</td>
<td>26 (72%)</td>
<td>21 (62%)</td>
<td>10% (-11%, 31%)</td>
<td>0.35</td>
</tr>
<tr>
<td>IV Antibiotics</td>
<td>12 (33%)</td>
<td>12 (35%)</td>
<td>-2% (-23%, 19%)</td>
<td>0.86</td>
</tr>
</tbody>
</table>
# Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>NAC (N=36)</th>
<th>Placebo (N=34)</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of AEs</strong></td>
<td>357</td>
<td>349</td>
<td></td>
</tr>
<tr>
<td><strong>AE rate</strong></td>
<td>0.43</td>
<td>0.43</td>
<td>1.00 (0.87, 1.16)</td>
</tr>
<tr>
<td><strong>Avg. N. AEs per person</strong></td>
<td>9.9</td>
<td>10.3</td>
<td>1.04 (1.22, 0.89)</td>
</tr>
<tr>
<td>Number (%) w/≥1 AE</td>
<td>33 (92%)</td>
<td>30 (88%)</td>
<td></td>
</tr>
<tr>
<td><strong>Total number of SAEs</strong></td>
<td>26</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td><strong>SAE rate</strong></td>
<td>0.03</td>
<td>0.04</td>
<td>0.88 (0.52, 1.49)</td>
</tr>
<tr>
<td><strong>Avg. N. SAEs per person</strong></td>
<td>0.72</td>
<td>0.85</td>
<td>0.87 (1.69, 0.44)</td>
</tr>
<tr>
<td>Number (%) w/≥1 SAE</td>
<td>11 (31%)</td>
<td>12 (35%)</td>
<td></td>
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</tbody>
</table>
## CFRSD Number of Respiratory Symptoms

<table>
<thead>
<tr>
<th></th>
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<th>Difference (95% CI)</th>
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<tr>
<td><strong>Screening</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>35</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.69 (1.78)</td>
<td>2.29 (1.22)</td>
<td>0.4 (-0.36 1.15)</td>
<td></td>
</tr>
<tr>
<td><strong>Week 12 (Change)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>N</td>
<td>32</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.00 (1.59)</td>
<td>0.34 (1.47)</td>
<td>-0.34 (-1.13 0.44)</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Week 24 (Change)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>30</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.43 (1.70)</td>
<td>0.59 (1.96)</td>
<td>-0.15 (-1.11 0.80)</td>
<td>0.75</td>
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# CFQ-R Respiratory Score

<table>
<thead>
<tr>
<th></th>
<th>NAC (N=36)</th>
<th>Placebo (N=34)</th>
<th>Difference (95% CI)</th>
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<tr>
<td><strong>Screening</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>36</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>70.76 (15.564)</td>
<td>72.06 (9.121)</td>
<td>-1.302 (-7.43 4.83)</td>
<td></td>
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<tr>
<td><strong>Week 12 (Change)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>31</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.09 (12.431)</td>
<td>-3.94 (11.670)</td>
<td>4.032 (-2.09 10.16)</td>
<td>0.19</td>
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<tr>
<td><strong>Week 24 (Change)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>30</td>
<td>31</td>
<td></td>
<td></td>
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<tr>
<td>Mean (SD)</td>
<td>-4.82 (11.556)</td>
<td>-4.48 (11.865)</td>
<td>-0.336 (-6.34 5.67)</td>
<td>0.91</td>
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Conclusions

• NAC, when taken with other standard CF therapies may slow loss of lung function.
  • NAC recipients maintained baseline lung function over 6 months
  • Placebo - 4 – 6% decline

• NAC does not appear to affect inflammation in the airways directly.
Potential Mechanisms of Action

- CSH
- Oxidases
- Antioxidant Defense Proteins
- ROS

Stanford Children's Health
Lucile Packard Children's Hospital Stanford
Potential Mechanisms of Action

• By providing a building block for GSH synthesis, NAC may modulate biological mechanisms involving GSH roles inside cells to maintain homeostasis (balance oxidants with anti-oxidants and decrease oxidative cell stress) \(^1\).

• NAC supplementation, by increasing body stores of GSH\(^2\), may modify inflammation\(^2, 3\), DNA transcription\(^3\), CFTR protein production\(^4\), or it may affect tissue fibrosis\(^5\).

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3. Haddad. Cellular Immunology 270 2011
5. Li, et al. Respiration 84 2012
Normalize Cell Functions

- Protein Synthesis/Transport
- Mitochondria
- Nucleus
Participating sites

Stanford University – Carol Conrad, MD
University of Utah – Barbara Chatfield, MD
University of Alabama, Birmingham Children’s Hospital – J.P. Clancy, MD
Yale University – Marie Egan, MD
Duke University – Peter Michelson, MD
National Jewish Hospital – David Nichols, MD
Columbia University – Lynne Quittel, MD
Children’s Hospital of Philadelphia – Ron Rubenstein, MD, PhD
Children’s Hospital of Pittsburgh – Jonathan Spahr, MD
Penn State, Hershey – Robert Vender, MD
University of Florida, Gainesville – Veena Antony, MD
## Acknowledgments

<table>
<thead>
<tr>
<th>CF Clinical Team</th>
<th>Support</th>
<th>Funding</th>
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<tr>
<td>Carol Conrad</td>
<td>Bioadvantex</td>
<td>CFFT</td>
</tr>
<tr>
<td>Richard Moss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colleen Dunn</td>
<td>Research Team</td>
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<tr>
<td>Zoe Davies</td>
<td>Rabindra Tirouvanziam</td>
<td>Marie Miglianico</td>
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<td>Leonore Herzenberg</td>
<td>Bahram Aram</td>
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<td>CF TDN</td>
<td>Leonard Herzenberg</td>
<td>Lakshmi Gudiputi</td>
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<tr>
<td>Bonnie Ramsey</td>
<td>Megha Makam</td>
<td>John Mantovani</td>
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<tr>
<td>Christopher Goss</td>
<td>Daisy Diaz</td>
<td>Claudia Weber</td>
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<tr>
<td>Jasna Hocevar-Trnka</td>
<td>Julie Laval</td>
<td>Yael Gernez</td>
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<tr>
<td>James Lymp</td>
<td>CFF</td>
<td></td>
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<tr>
<td>Kimberly Gilmore</td>
<td>Preston Campbell</td>
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</table>
Stanford CF Patients Are

AWESOME!!!
Redox Regulation of TNFα and Inflammation

• The pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α, contribute to the exacerbation of pathophysiological conditions in the lung.
• Inhibition of GSH synthase by ROS, which results in cellular depletion of GSH, increase in H2O2 and ·OH
  • ROS stimulate cytokine secretion via DNA transcription activation when TNF α is able to enter nucleus and activate cytokine transcription.
Activation of NF-κB is Redox-Sensitive

- The regulation of inflammatory cytokine gene transcription involves the redox-sensitive (NF-κB) in macrophages AND alveolar epithelium.
  - NF-κB is activated when cytosol IκB (a cytosolic constitutive inhibitor of NF-κB) levels drop
NAC Inhibits Fibrosis by Inhibiting LOX

- Rat model IPF
- LOX oxidizes lysine residues in collagen and elastin leading to the formation of crosslinks essential for stabilization of the extracellular matrix
- Association of pulmonary fibrosis with elevated LOX activity
- LOX inhibitor prevented BLM-induced pulmonary fibrosis in hamsters.

Li, et al. Respiration 84 2012
Inhibition of Interstitial Fibrosis

- Increased cellular GSH decreased levels of LOX protein species and catalytic activity in vitro
- Elevation of cellular GSH induced reduction of LOX activity in cells exposed to cigarette smoke
- NAC may ameliorate IPF at least in part via downregulation of LOX

Li, et al. Respiration 84 2012
NAC Increases Cl⁻ Efflux from CFBE

- The effect of NAC on Cl⁻ transport was measured by Cl⁻ efflux measurements and by X-ray microanalysis.
- Cl⁻ efflux from CFBE cells was stimulated by NAC in a dose-dependent manner.

NAC Increases Cl⁻ Efflux from CFBE

- Immunocytochemistry and Western blot experiments revealed expression of CFTR channel on CFBE cells after treatment with NAC.

The Effect Of N-Acetylcysteine On Chloride Efflux From Airway Epithelial Cells

(A, B) CF cells treated with NAC

(C) CF cells NOT treated with NAC

- Immunocytochemistry of CFBE cells treated with 10 mM NAC for 4 h, then stained to look for CFTR protein
NAC Corrects Autophagy

• Newly synthesized CFTR molecules are first monitored for folding status by molecular chaperones

• F508del mutation causes the protein to be misfolded and prematurely degraded through the ER-associated proteasomal degradation (ERAD).

• Chaperone-mediated selection is coupled with ubiquitination of misfolded CFTR in the ER

Aggresome Formation in CF Due to
misfolded F508del
Correction of protein trafficking of F508del.