Aerosolized Alpha-1-Antrypsin

M. Brantly, MD
University of Florida
USA

Concepts of Inhaled Alpha-1-Antitrypsin (AAT)

1.Normally, AAT travels to the lung from the blood into the space (interstitium) between the capillary to the air sac (Alveoli)

2. Inhaled AAT must travel from the lung to through interstitium to the blood

3. For AAT to get to the Alveoli the particles of AAT have to be less than 3 um

Concepts of Lung Damage

Lung damage (emphysema, bronchitits and bronchectasis) are caused by inflammation as a result of smoke, infection and pollution

Inflammation is mediated by cells (PMNs) that normally fight infections these cell release neutrophil elastase (NE) that damage the lung

More cells and NE cause the damage to the lung

Inhaled AAT

Must get in the alveoli

Must be functional

Must inactivate NE

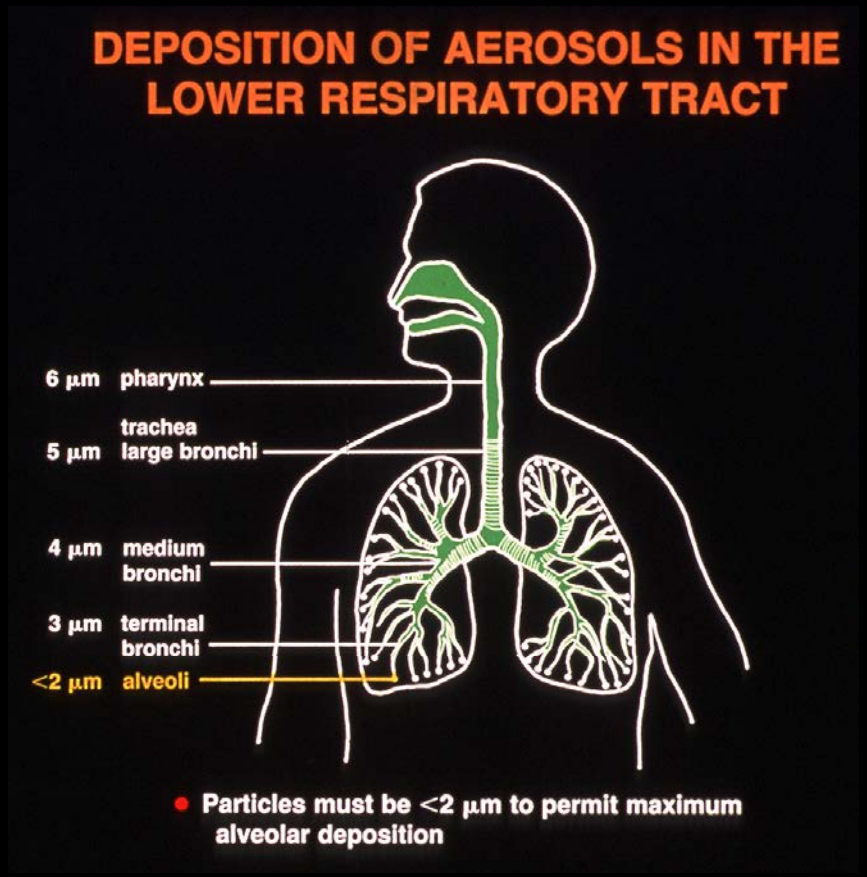
Must decrease neutrophils (PMN)

TO STOP LUNG DAMAGE

Potential of Aerosolized AAT

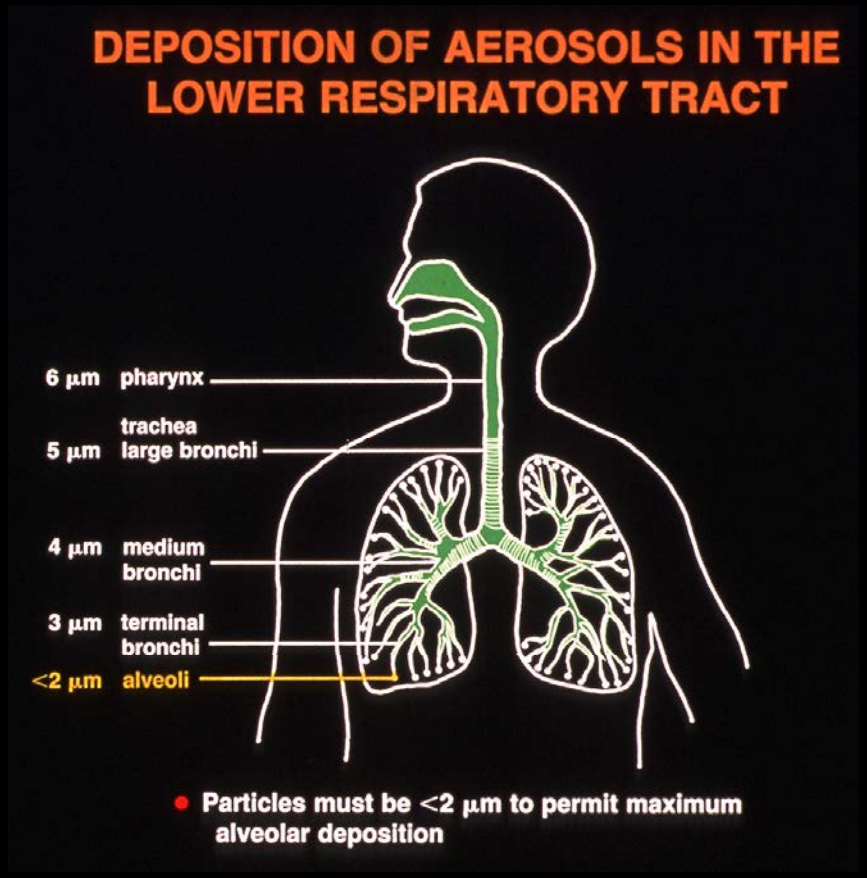
- IV Augmentation Tx is not a Magic Bullet and Require IV Access
- Most IV AAT Does Not Reach the Lung
- IV AAT that Does Reach the Lung is in low normal range in Epithelial Lining Fluid

- Ease of Use (no infusions) Potential more Effective TX
- Direct Delivery to Airway and Lower Respiratory Tract
- Potential to Deliver High Dose to the Lung
- Possibility of Using in Aerosol in other Individuals with COPD



Components Necessary to Develop Aerosolized AAT for the Clinic

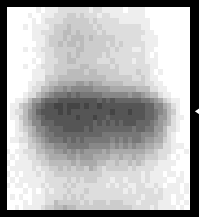
- Highly Purified AAT (Aralast NP, Zemaira, Prolastin MP, Kamada API, Arriva rAAT)
- High Efficiency Deep Lung Delivery Devices
- Determine the Safe and Appropriate Dose of AAT
- Robust Outcome Variables Appropriate for Rare Disease Studies
- Low Toxicity
- Robust Surrogate Markers for Phase I/II
- Demonstrate that Aerosolized AAT Reaches the interstitial Space



Elements Necessary for Development of Aerosolized AAT

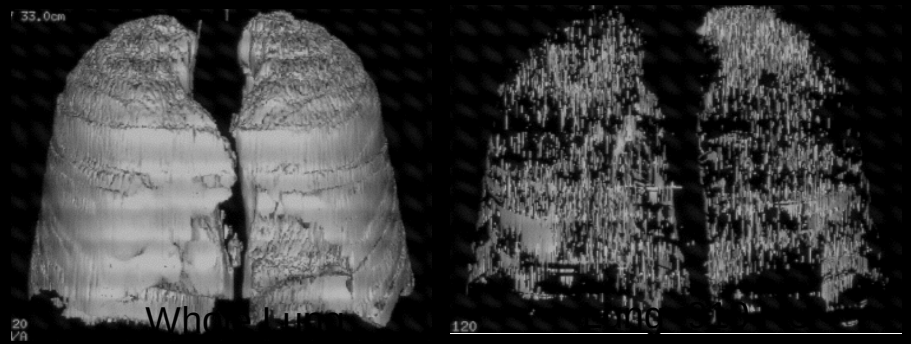
High Efficiency Aerosol Delivery Devices

Highly Purified AAT



Aerosolized AAT

Robust Outcome Variables



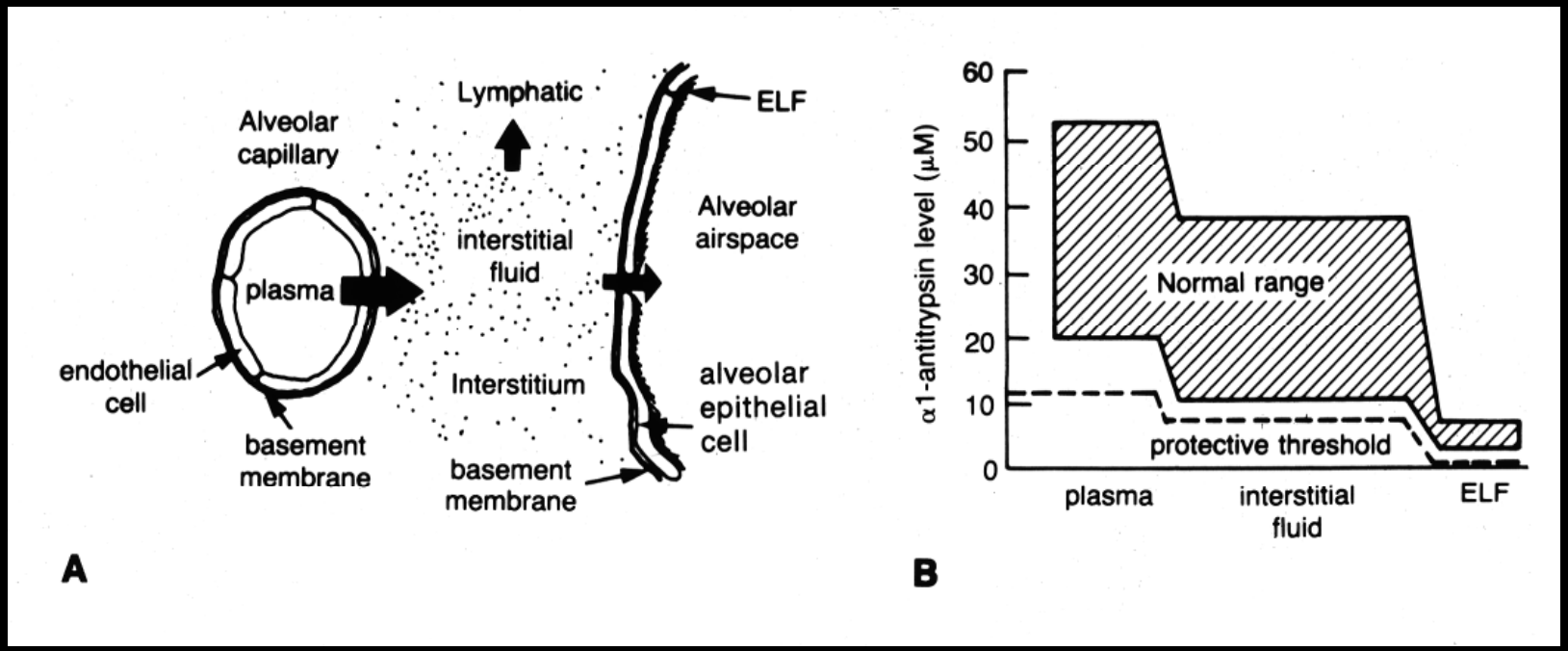
Some of the Aerosolized AAT Studies

1) Study Demonstrating Lung Inflammation in AAT Deficient Individuals (Lower Respiratory Tract and Airways) NIH intramural program (Inflammation in the Respiratory Track)
2) Phase 1/2 Study using 250 mg of rAAT (Sheep) CRC 1999-2001 (AAT Reduces Inflammation)
3) Phase 1 Study-Dose Escalation using AAT (Human Plasma Purified) in a Dry Powder-CRC 2001-2003

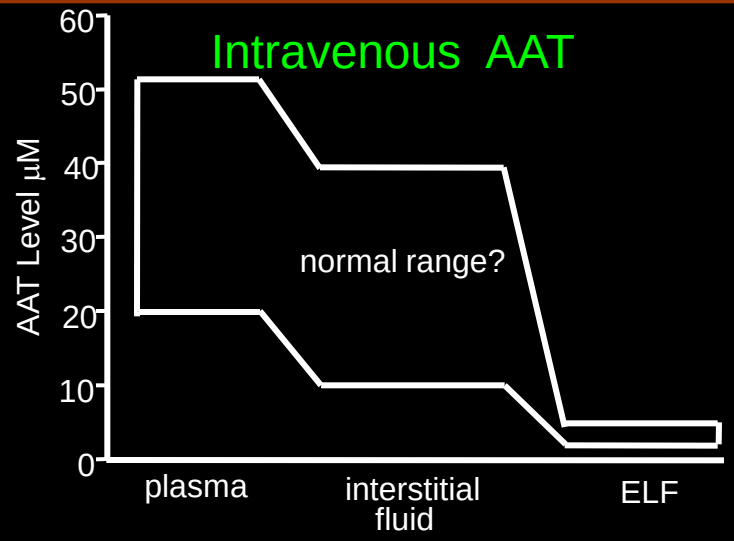
   (High Efficiency Device Can Deliver Large Amounts of AAT to the Lower Respiratory Track)
4) Phase 1 Study using rAAT (Yeast) CRC 2004-2005

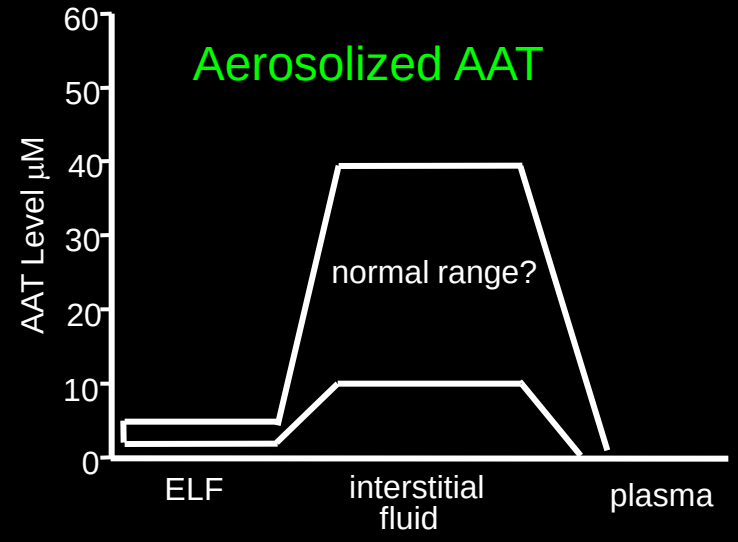
   (qD Dosing can Delivery Large Amounts of AAT to the Lung)

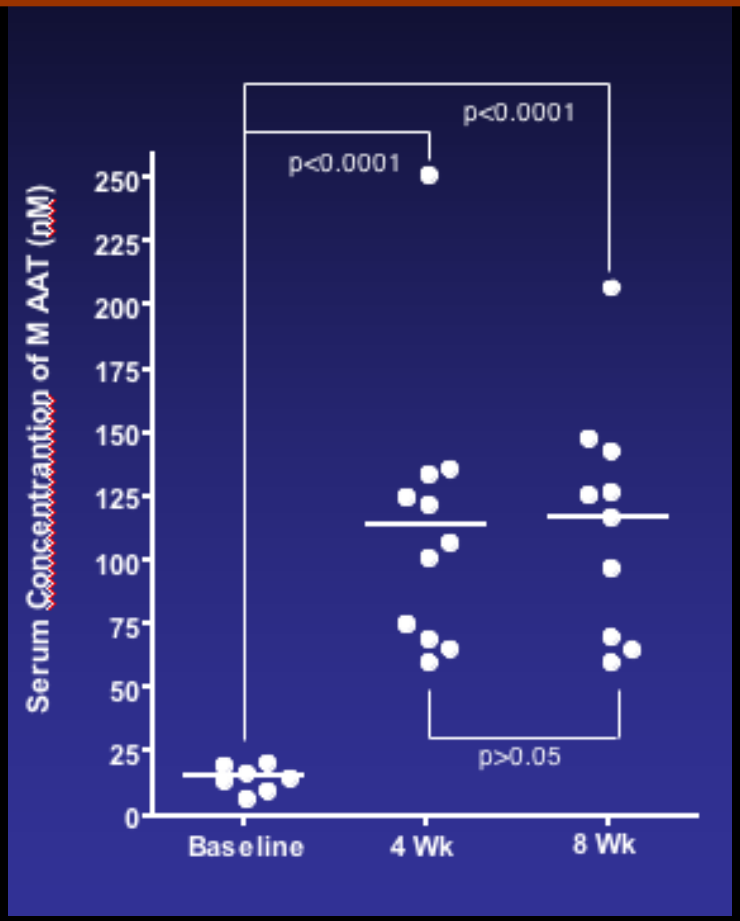
Does Aerosolized AAT Fill the Interstitial Space?



Does Aerosolized AAT Reach the Interstitium?







- Aerosolized AAT reaches the plasma and therefore crosses into the interstitium

Kamada-API for Inhalation, Phase II Study

Design

- 36 subjects with documented alpha-1 antitrypsin deficiency will be enrolled into two dose groups of 80 mg/day and 160 mg/day.
- Each group will be randomized per site at a ratio 2:1 vs. a matching dose of placebo. Each group and their matching placebo will be enrolled in separate sites.

Site	Subjects on active drug	Subjects on placebo drug	Double blind treatment period	Open label treatment period
1	12	6	12 week 80 mg active AAT or placebo	12 week 160 mg active AAT
2	12	6	12 week 160 mg active AAT or placebo	12 week 160 mg active AAT

Investigational Product and Dosing

- Investigational product is supplied in sterile, single-use glass vials containing 4 mL of a 2% ready-to-use solution of active alpha-1 antitrypsin (nominal dose of 80 mg) and matching placebo

Inhalation will be performed in the following manner:

Double blind period:

SITE 1 (80 mg "Kamada-API for Inhalation" or Placebo)	SITE 2 (160 mg "Kamada-API for Inhalation" or Placebo)
One session in the morning (before noon)	One session in the morning (before noon)
	One session in the evening

Study Endpoints

Primary

- Levels of antigenic and functional AAT in ELF

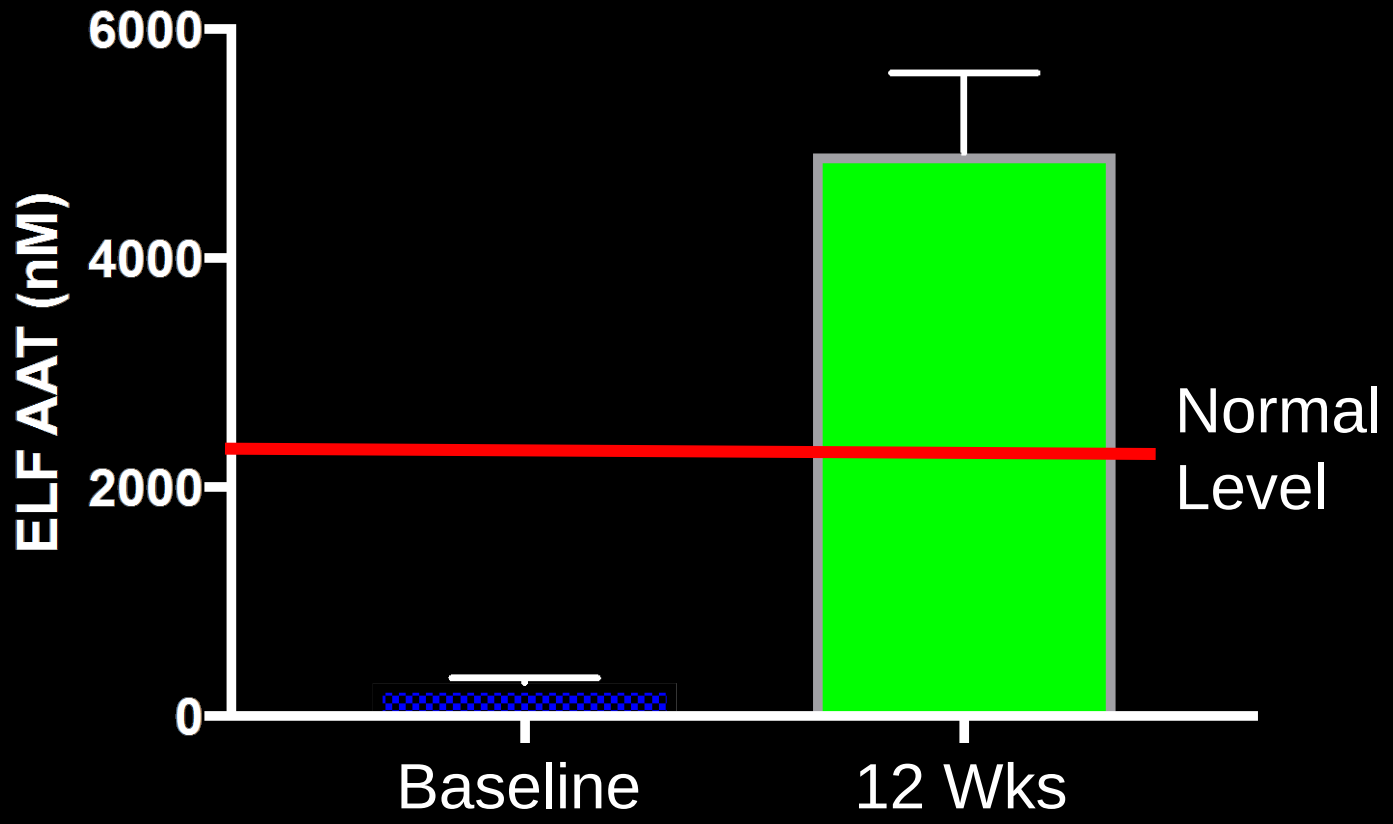
Secondary endpoints

- Safety and tolerability
- Levels of antigenic and/or M-specific AAT in serum
- AAT-NE complexes in ELF
- Neutrophil elastase concentration in ELF
- Neutrophil count in ELF

eFlow Aerosol Device

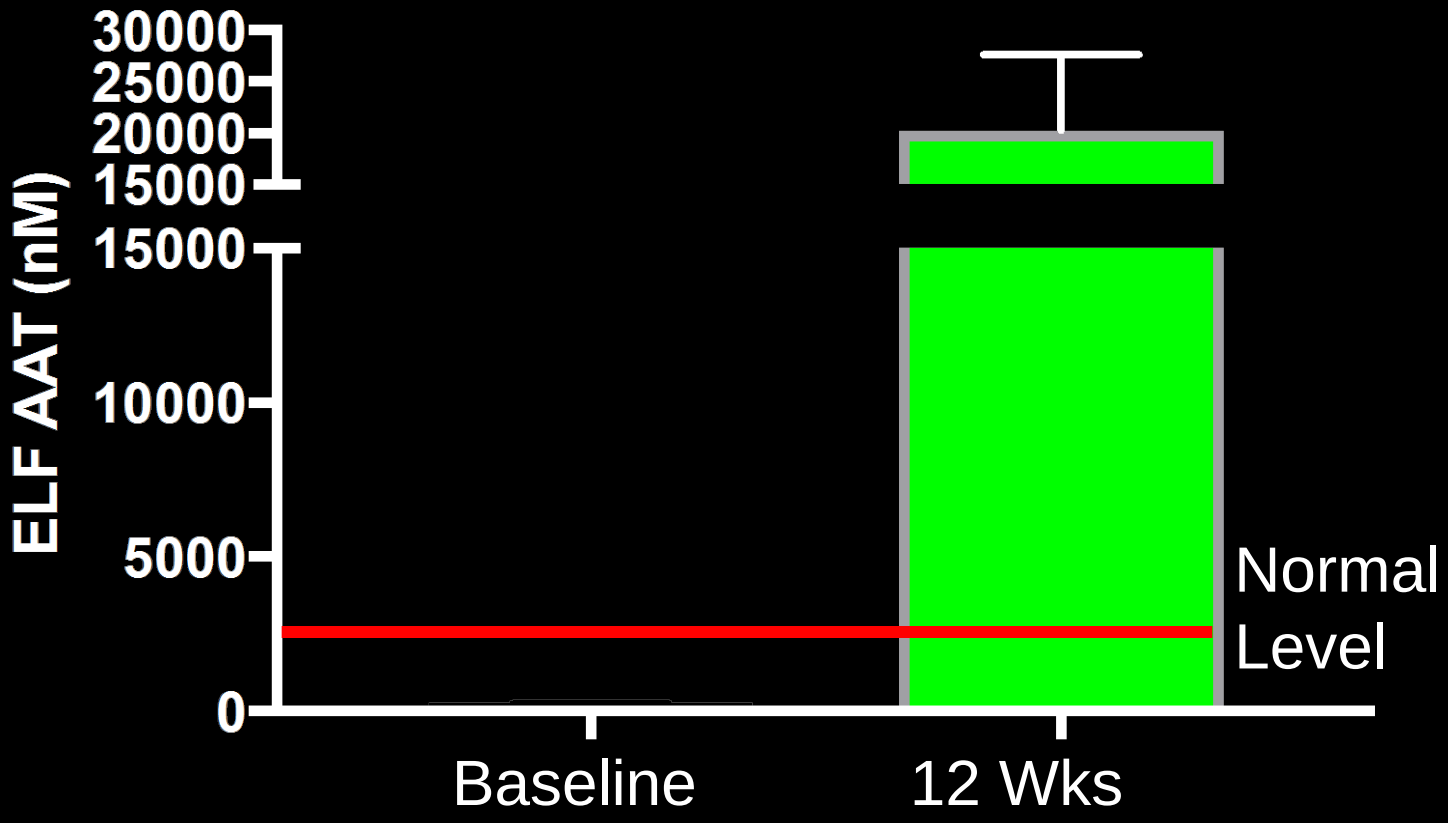
Figure 4-2 eFlow® for use with "KAMADA-API for inhalation"

Lung Level of AAT 80 mg Daily



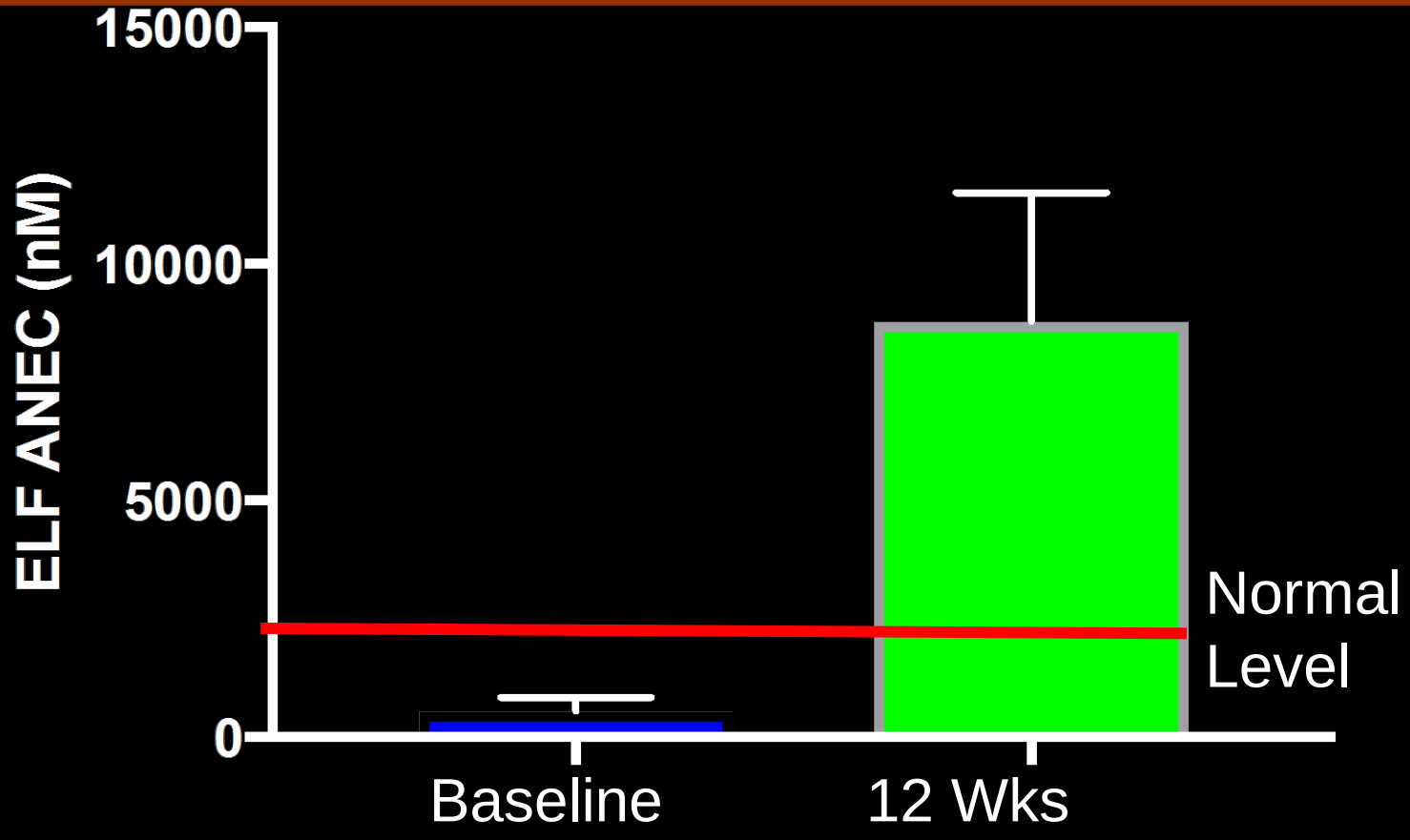
After 12 weeks of 80 mg of inhaled M AAT daily
Plasma ELF (Lung Levels) are 17x higher than baseline

Lung Level of AAT 160 mg Daily



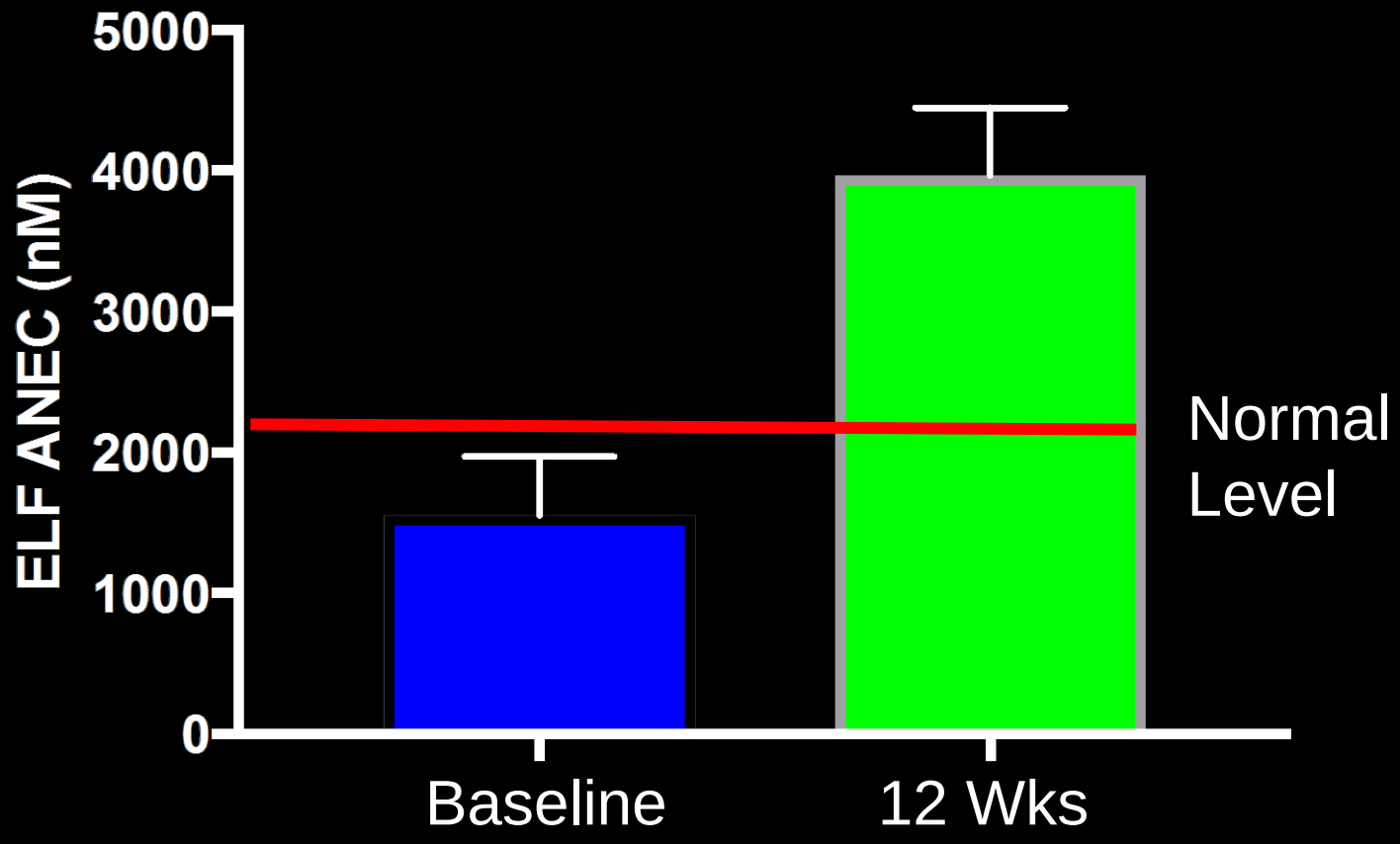
After 12 weeks of 160 mg of inhaled M AAT daily
Plasma ELF (Lung Levels) are 100x higher than baseline

Lung Level of ANEC 160 mg Daily



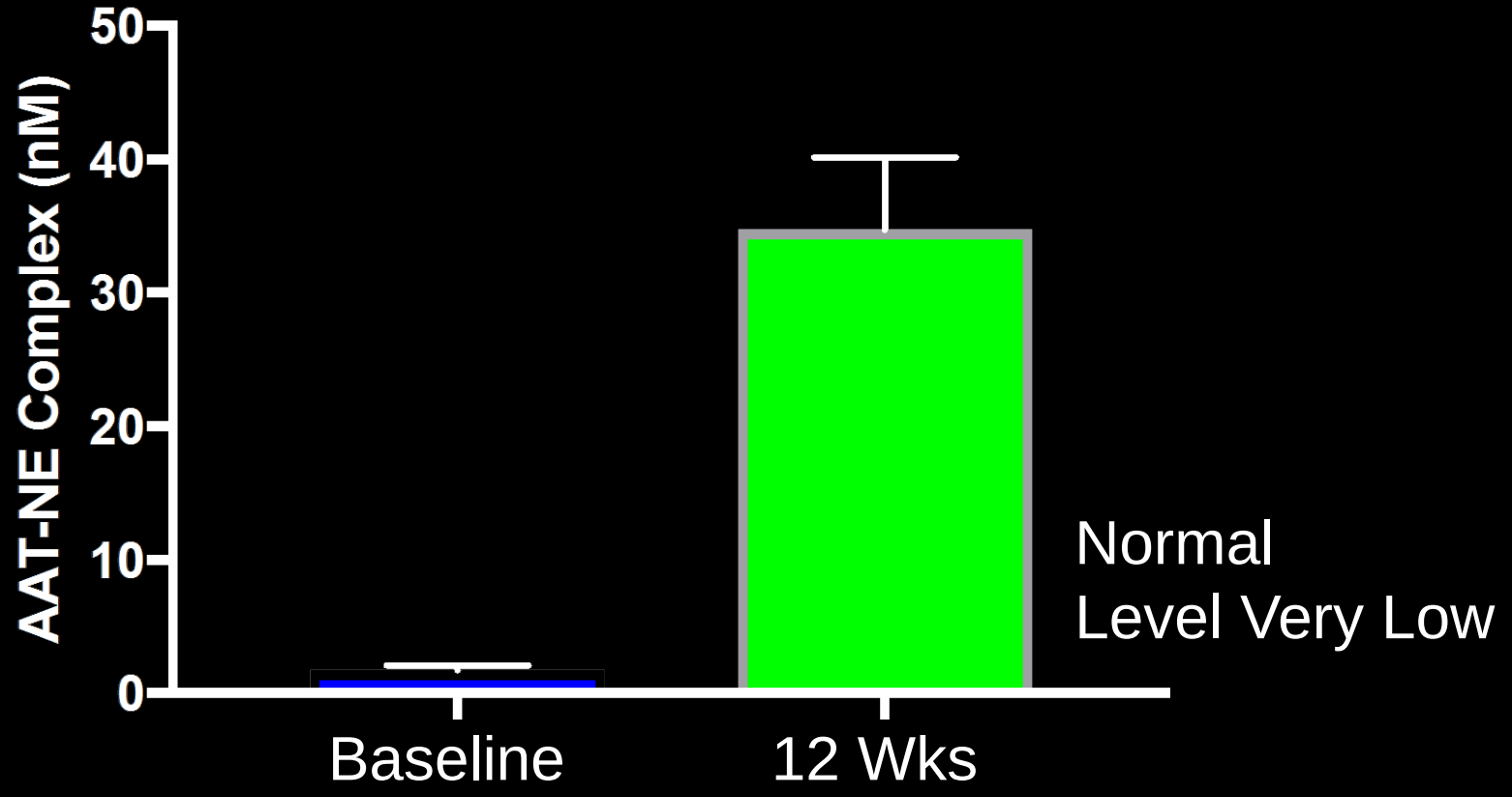
After 12 weeks of 160 mg of inhaled M AAT daily
ELF ANEC (Lung Levels) are 16x higher than baseline

Lung Level of ANEC 80 mg Daily



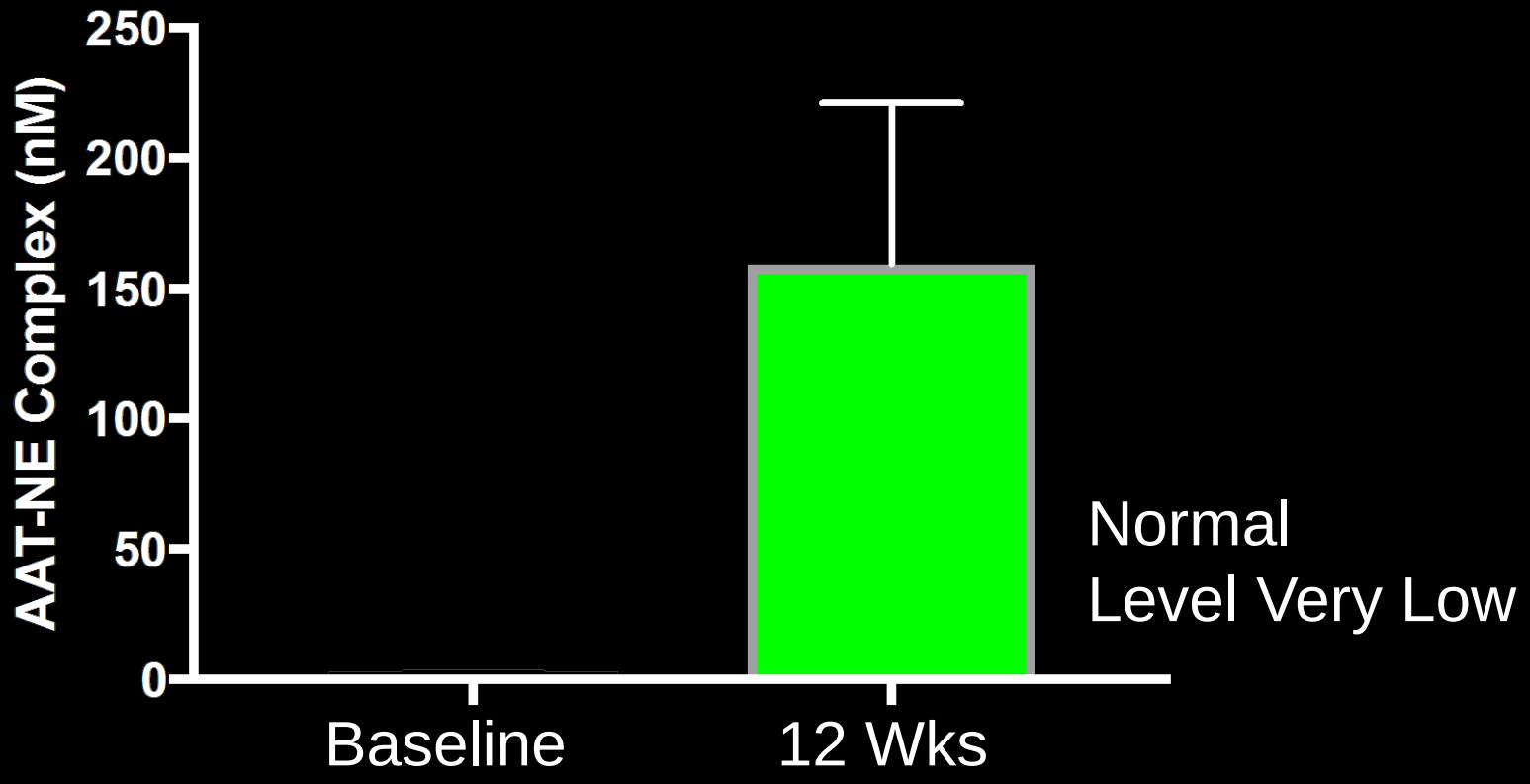
After 12 weeks of 80 mg of inhaled M AAT daily
ELF ANEC (Lung Levels) are 2x higher than baseline

Lung Level AAT-NE Complex 80 mg Daily



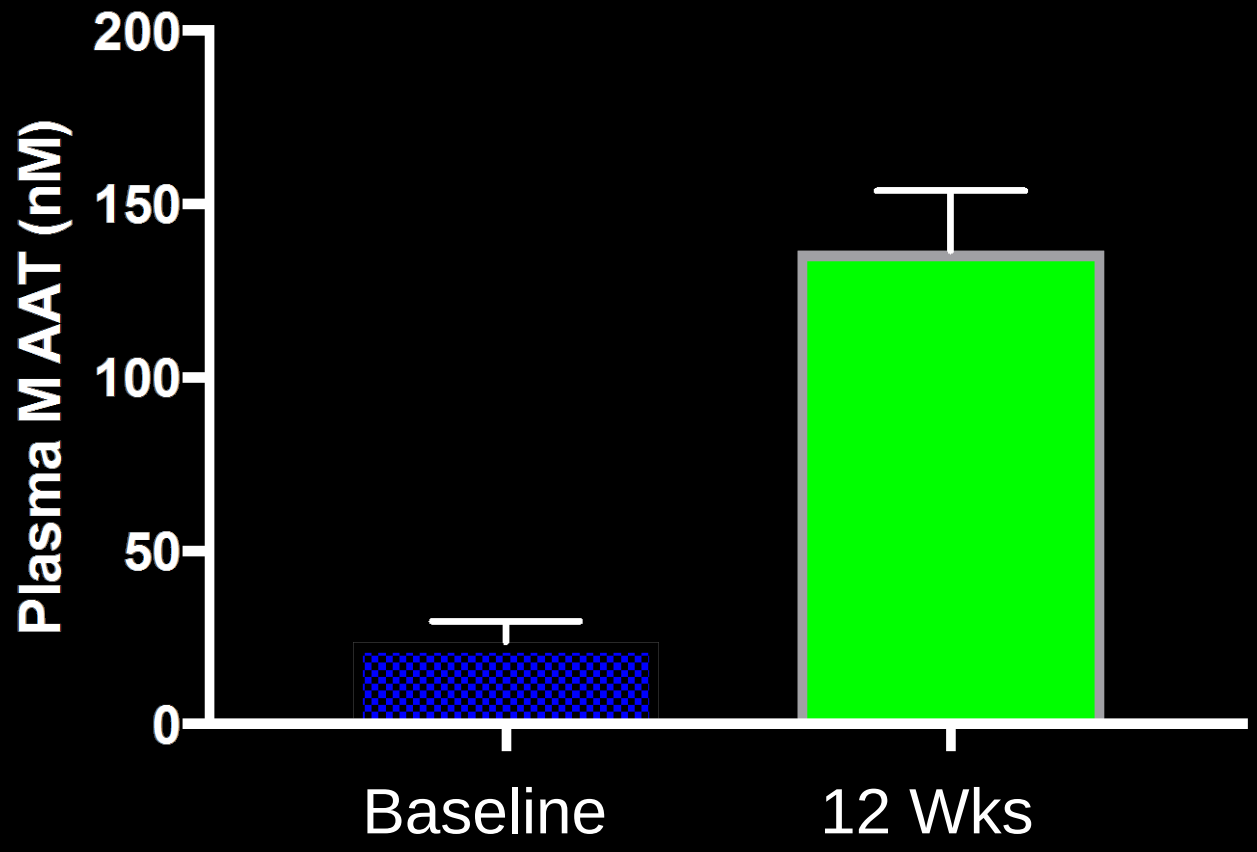
After 12 weeks of 80 mg of inhaled M AAT daily
ELF AAT-NE Complexes are many fold higher than baseline

Lung Level AAT-NE Complex 160 mg Daily



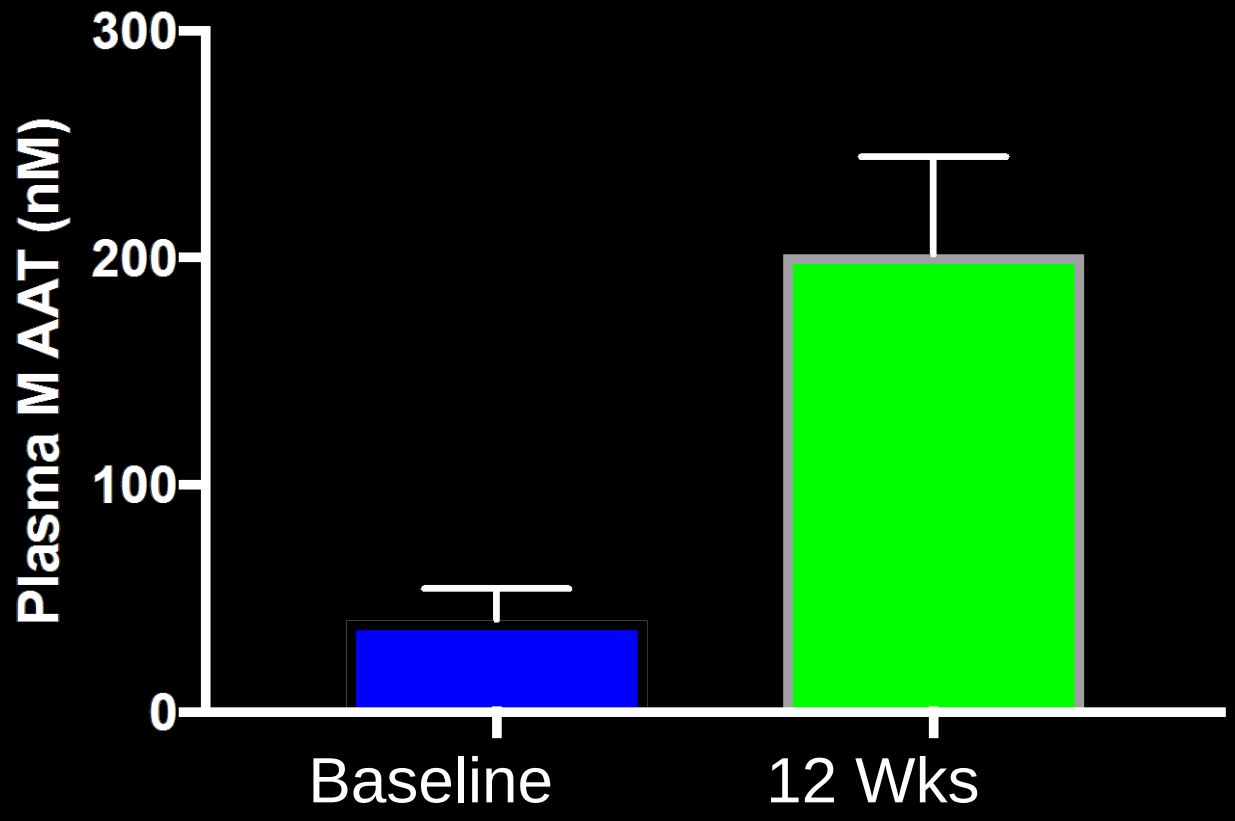
After 12 weeks of 160 mg of inhaled M AAT daily
ELF AAT-NE Complexes are many fold higher than baseline

Plasma M AAT 80 mg daily



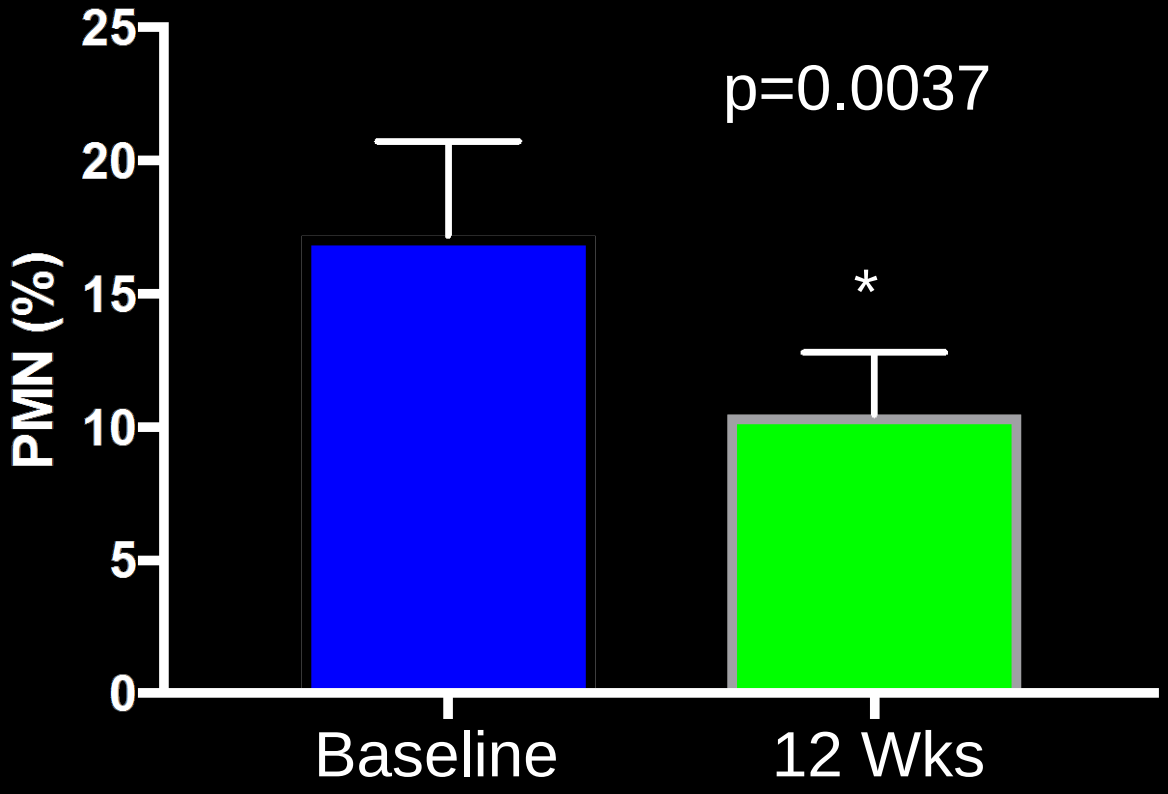
After 12 weeks of 80 mg of inhaled M AAT plasma MAAT level are 6 times higher than baseline

Plasma M AAT
160 mg daily



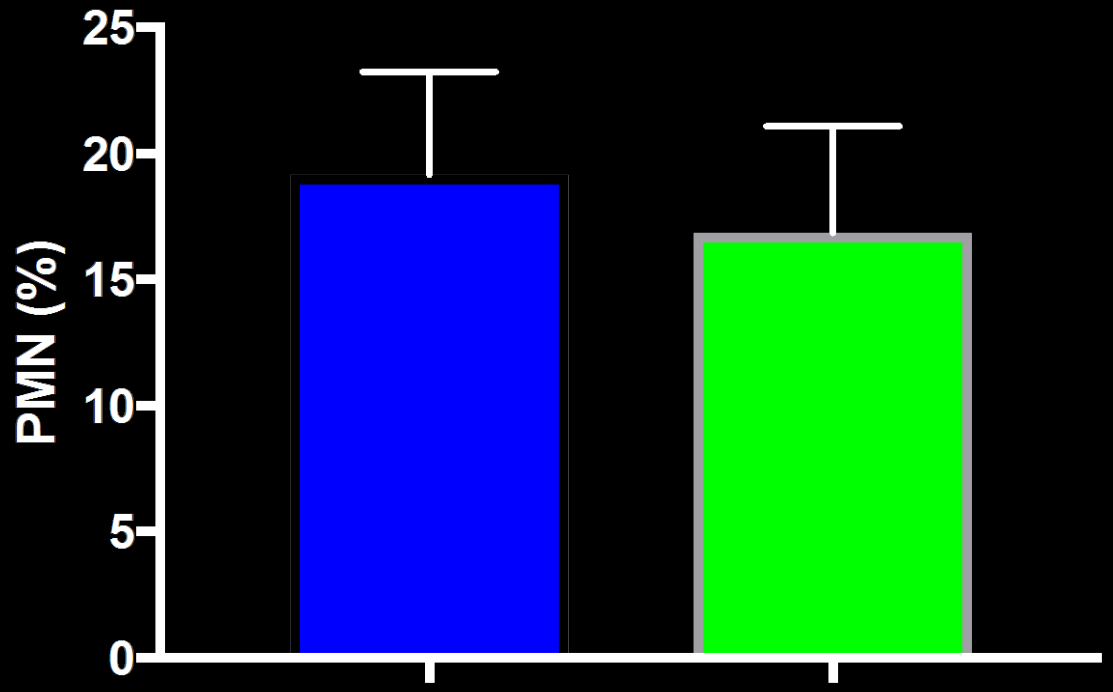
After 12 weeks of 160 mg of inhaled M AAT plasma MAAT level are 8 times higher than baseline

PMN %
80 mg Daily



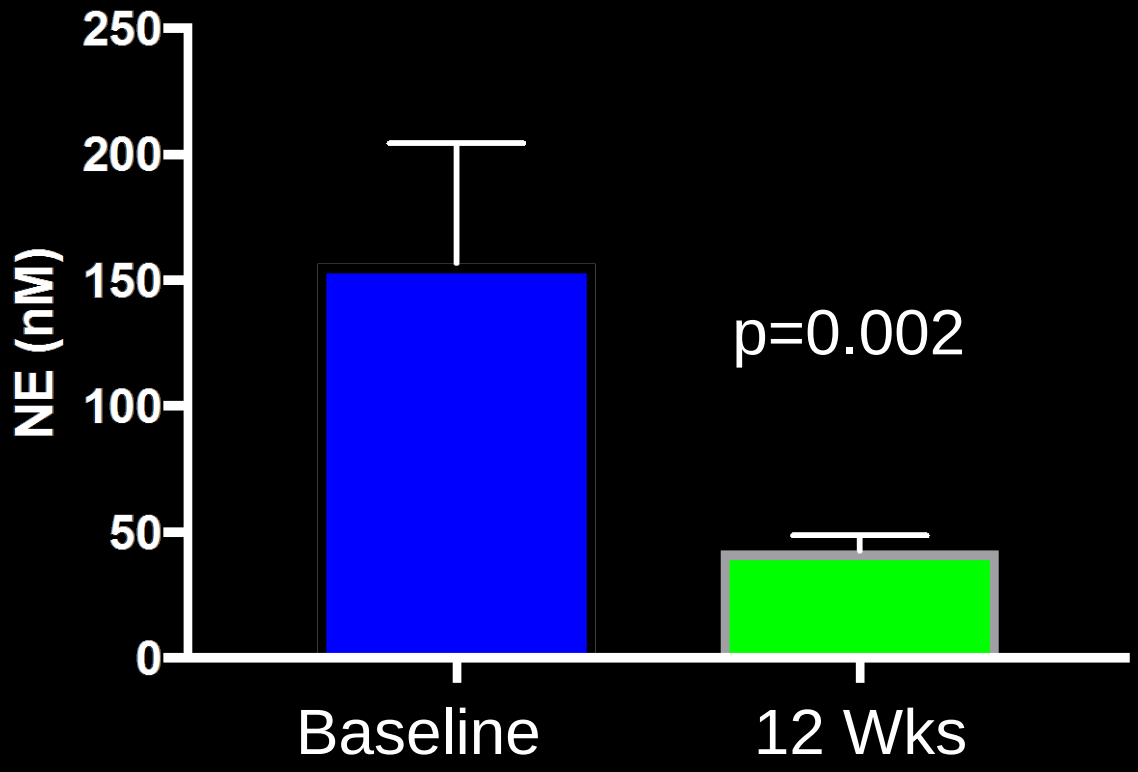
After 12 weeks of 80 mg of inhaled M AAT
PMN % significantly than lower than baseline

PMN %
160 mg Daily



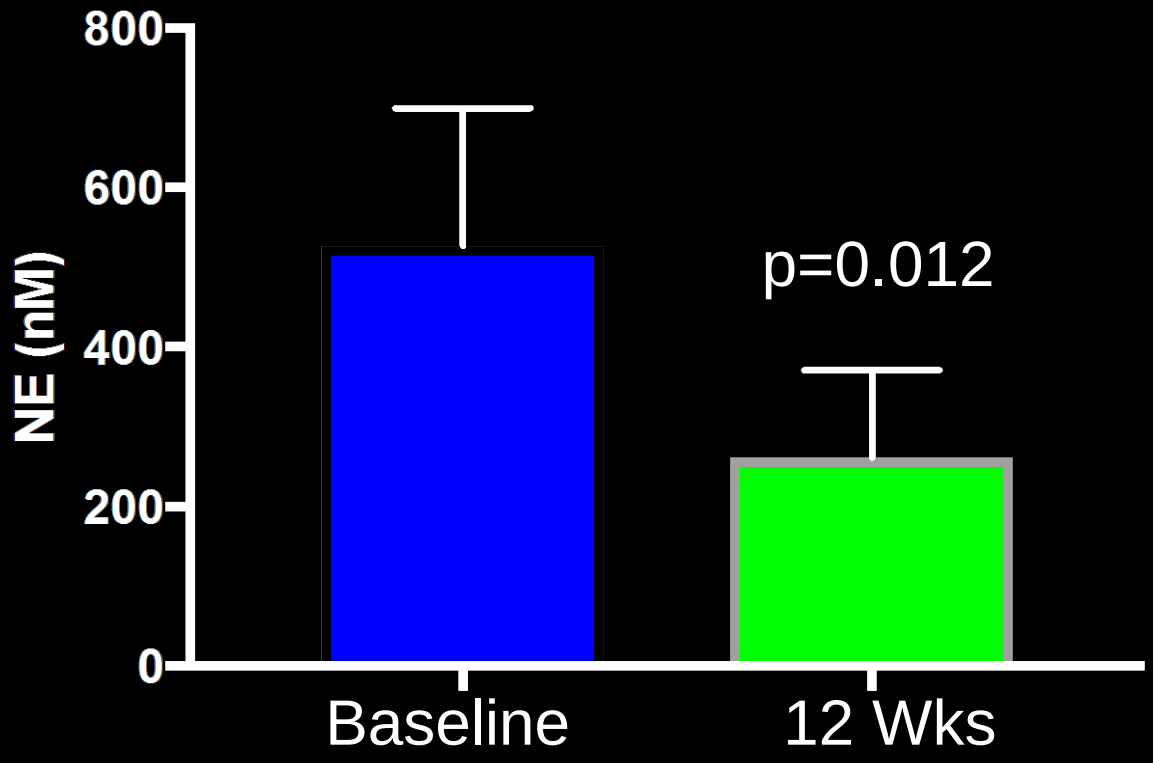
After 12 weeks of 160 mg of inhaled M AAT
PMN % non-significant change from baseline

Lung Level of NE 80 mg Daily



After 12 weeks of 80 mg of inhaled M AAT
Lung NE was significantly than lower than baseline

Lung Level of NE
160 mg Daily



After 12 weeks of 80 mg of inhaled M AAT
Lung NE was significantly than lower than baseline

Conclusions

- Highly purified AAT available
- Excellent deep lung delivery devices
- AAT demonstrated to have anti-inflammatory effect in lung
- Aerosolized AAT crossed the interstitial space
- AAT get into the lung
- AAT inactivates destruction NE
- AAT Reduces inflammation