BREATH OF LIFE: INHALABLE MRNA THERAPEUTICS FOR AATD

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Acknowledgement: Cheryl (biology & chemistry) researched the problem of AATD and decided the idea of inhalable mRNA. Zhentao (physics & engineering) worked on the mechanics of the inhaler and made sure our solution was scientifically feasible. Louisa (medicine & economics) worked on the human biology behind the solution, clinical trials and accessibility to the public. Cheryl & Zhentao (art) made the illustrations.

Problem: AATD

AATD (alpha-1 antitrypsin deficiency) is a genetic disease affecting the lung caused by two copies of a mutated SERPINA1 gene. In a healthy body, the liver makes a protein called AAT (alpha-1 antitrypsin) which is released into the bloodstream and protects the lungs against destructive elastase enzymes released by neutrophils. Without AAT, fragile alveolar tissues in the lungs are easily damaged. This risk increases with smoking and lung infections.

Impact:

Early symptoms include shortness of breath, chronic cough, chest pain and persistent tiredness. Patients are much more likely to develop COPD and emphysema in their early years. The condition leads to a progressive deterioration in lung health which may eventually become fatal.

AATD affects around 1 in 2500 people. Globally, AATD affects 3.4 million people; this is likely an underestimate as AATD is often underdiagnosed or misdiagnosed.

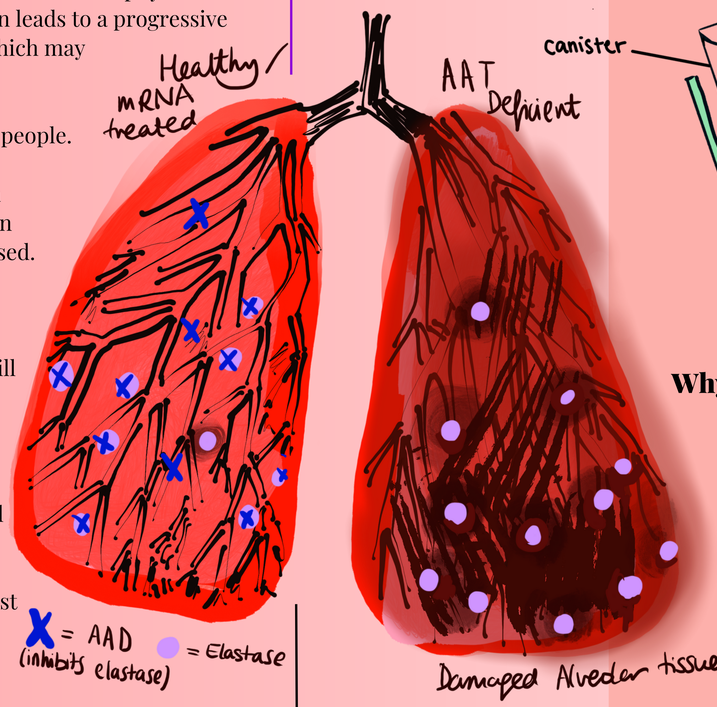
Target Audience

Regular AAT mRNA therapy will prevent AATD patients from suffering lung damage and developing lung diseases. However, most patients are not diagnosed with AATD until their conditions are rapidly deteriorating. This is when AAT mRNA therapy will be most effective, as it stabilises symptoms and prevents end-stage lung diseases from developing.

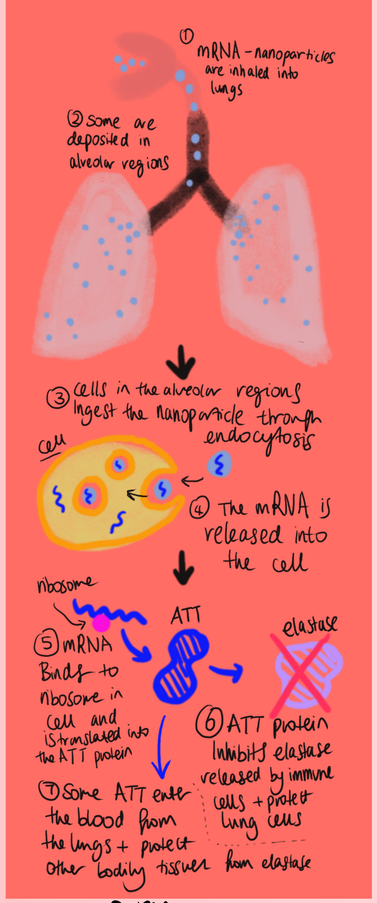
Our Innovation

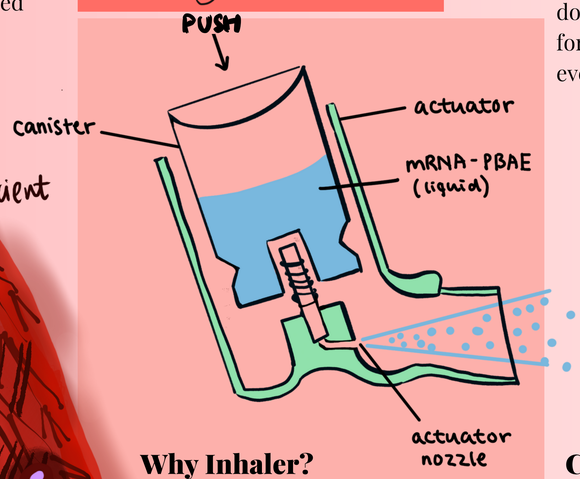
We use the principles of mRNA therapy to treat AATD. Our innovation creates a synthetic mRNA molecule complementary to the SERPINA1 gene, which encodes the AAT protein. Once the mRNA is released into the cell, the ribosome translates the mRNA into functional AAT proteins that protect the lung cells.

Our solution departs from existing therapeutics through the way the mRNA is delivered. We took inspiration from a paper [1] that developed an inhalable mRNA therapy for cystic fibrosis. We will contain the mRNA within a nanoparticle carrier made of poly(beta amino-esters). The polymer stabilises the mRNA during inhalation. The nanoparticle can be freeze-dried into a fine powder, which means the therapy can be delivered via an inhaler.



How Our Solution Works





Why Inhaler?

Inhalers are a non-invasive and easy-to-use method for delivering drugs into the lungs. It allows the nanoparticle carrying the mRNA to reach the innermost alveolar tissues due to their small particulate size. Inhaler will be used once a week and refilled with mRNA once every two months at the clinic.

Limitation of current AATD treatments:

Liver transplant

- only offered for only a small minority of patients with end-stage liver diseases
- unavailable for patients with primarily lung symptoms.

Augmentation therapy: AAT protein is injected into veins to slow down the progression of COPD and emphysema

- **Expensive** (annual cost = £18,100) as AAT has to be isolated from the plasma of healthy human donors. It is not available in the UK as it has not been approved by NICE, the National Institute for Health and Care Excellence.
- **Inconvenient**: involves weekly IV infusion given by a healthcare professional. There is also the risk of an allergic reaction.

Gene therapy: using viruses to permanently edit the mutated gene

- High risk of immune response
- Risk of mutations and cancer.

Novelty and Vision

Our vision is to create an affordable, easy to use and effective solution to AATD.

- Our solution is **low cost**, evening out healthcare inequality as currently augmentation therapy can only be afforded by the affluent.
- Inhalable mRNA is much **less invasive** and can be done at home. This makes the treatment accessible for those who cannot afford to go to the hospital every week.

Technological Innovation:

- mRNA is directly inhaled, which means a larger concentration reaches the lungs
- This means that the unstable mRNA molecule is less likely to break down before reaching the cells, increasing effectiveness
- Beta-amino esters are biodegradable with minimum side effects

Cost, Affordability and Availability

Based on mRNA vaccines, we have estimated costs to be

- £0.42 to manufacture a dose (lasting around 2 months)
- £2.48 per inhaler

Due to the low cost of the therapy and its ability to drastically improve quality of life and life expectancy, we anticipate that NICE will approve it for the NHS, enabling the treatment to be provided for free to all AATD patients.

Feasibility

Scientific:
MIT researchers have confirmed the success of inhaled mRNA therapeutics by encoding luciferin (a glowing bioluminescent protein) in mRNA molecules. They showed that protein are produced within 24 hours and that the proteins are uniformly distributed within the lung.

Research also shows that AAT proteins produced through the injection of mRNA into cells are highly functional and high in concentration.

Manufacturing:
The mRNA manufacturing process is relatively simple, versatile and well established due to the prevalence of mRNA vaccine facilities [2].

Clinical Trials

We will assess the safety and efficacy of our therapy through:

Pre-clinical trials

We will test the system on human lung organoids, or "mini-organs-in-a-dish". We will also conduct trials on animal models of AATD.

Clinical trials

We will begin testing with a small group of healthy volunteers at low dosage to identify any potential side effects. Then, the trial will extend to several hundred individuals diagnosed with AATD. We will follow through from phase 1-4 of clinical trial to assess the treatment efficiency, optimal dosage and submit results to NICE for approval.

Ethical Principles:

We will ensure informed consent by making participants fully aware of the study's purpose, risks, benefits, and their right to withdraw at any point. We will rigorously protect participant confidentiality and data privacy.

Public Acceptability

Public acceptance will be fostered by robust safety trials, regulatory approval, and transparent communication of these processes. We will work with doctors to subscribe the therapy to AATD patients who will benefit from it, which will further create trust with patients. We will also launch education campaigns to raise awareness about AATD and increase early diagnosis.

References: