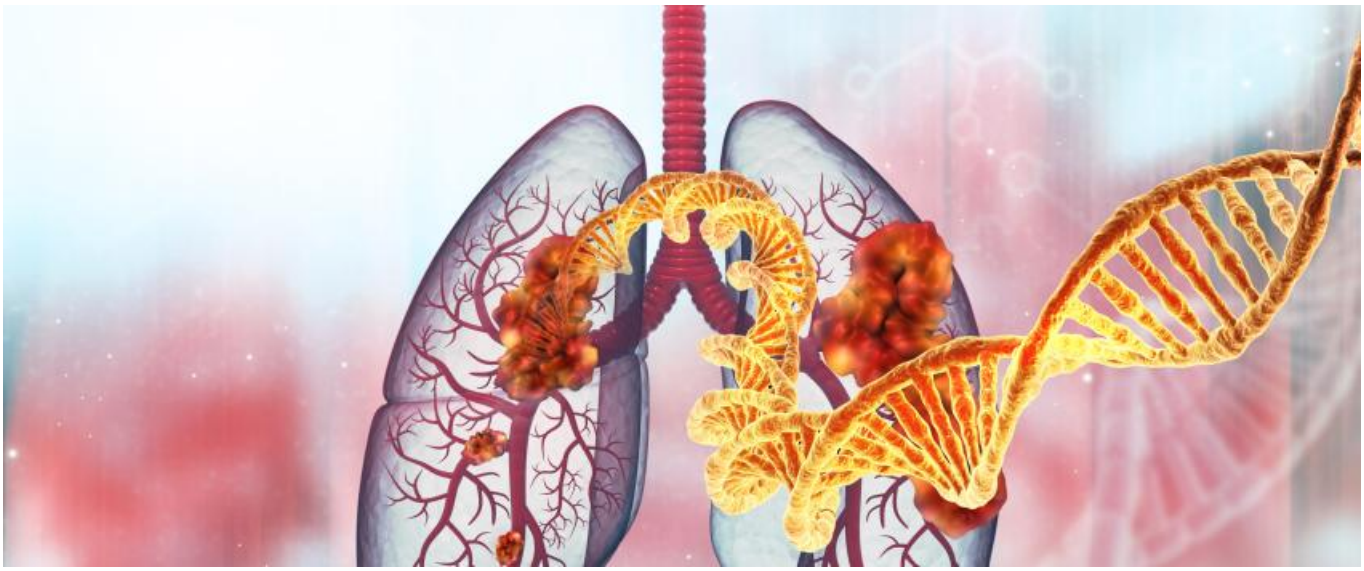
Evaluate Vantage

February 24, 2023

# Spotlight – Cystic fibrosis developers take a deep breath

Elizabeth Cairns



## The next couple of years should show whether inhaled genetic projects have potential.

Last month Vertex kicked off the promised trial of its inhaled mRNA formulation for cystic fibrosis – a courageous move, given that this mechanism has failed in the past. In fact human trials are underway for several inhaled genetic medicine projects that aim to correct or replace the faulty CFTR gene which causes the disease.

Most are gene therapies, though antisense agents and, further down the pipeline, exon skippers and RNA interference candidates are also present. But it is probably fair to say that all these approaches, clinical and preclinical, have either disappointed previously or remain unproven.

Vertex's decision to start a clinical trial of VX-522, the mRNA therapeutic it has developed with Moderna, means it believes it can do better than Translate Bio. Translate's inhaled mRNA, designed to deliver mRNA encoding functional CFTR protein directly to the lung epithelium, failed to show any signs of efficacy in early trials two years ago.

Translate was acquired later in 2021 by Sanofi, but the French group is no longer looking at mRNA therapeutics for cystic fibrosis. Several companies are, however – though Vertex is the only one to have entered the clinic.

The analysis below concerns only agents intended to address cystic fibrosis itself by genetic means. Inhaled antimicrobials to treat the infections that plague cystic fibrosis patients are excluded, as are generally anti-inflammatory approaches.

### Human trials

The most advanced among this cohort is 4D-710, 4D Molecular Therapeutics' gene therapy. In November this yielded interim data from the first three patients in a phase 1/2 trial, indicating decent tolerability and successful transfection of the CFTR gene, with all 11 endobronchial lung samples taken from the three patients positive for the gene.

4D is currently enrolling a further 3-6 patients into the second cohort of the study, with further data due this year.

Meanwhile, Krystal Biotech has started not one but two human trials of its redosable inhaled gene therapy, KB407. These could read out next year, perhaps in a similar timeframe to Vertex's new study. The trials use measures of lung function as secondary endpoints.

The other approach in the clinic is antisense, in the shape of Splisense's oligo SPL84. This is aimed at patients with a specific and very rare mutation – the 3849+10 kilobase (Kb) C→T splicing mutation, found in an estimated 0.2% of cystic fibrosis patients. A smaller molecule than the mRNA projects, SPL84 can enter the cell by itself once inhaled, Splisense believes, and can thus dispense with a lipid nanoparticle carriers. The phase 1/2 trial will evaluate "preliminary efficacy" as well as tolerability, though no date has been given for when results might become public.

Here too the history is not encouraging. Both Arrowhead and Ionis have walked away from phase 1-stage inhaled RNA interference or antisense projects, in both cases after red flags were seen in preclinical trials. Arrowhead, at least, is trying again, with a second generation version in preclinical development.

**Earlier**

Many of the preclinical candidates are also either mRNA or gene therapies – but there are some more leftfield mechanisms under investigation.

Eloxx Pharmaceuticals, for example, is developing a small molecule, ELX-02, which binds to the ribosome and prevents premature stop codon reading, caused by nonsense mutations, that leads to the production of truncated, non-functional CFTR protein.

Last September the company admitted that the subcutaneous form of the agent had failed in phase 2, and terminated development. It believes that the inhaled form could have "more than one hundred times lung to plasma exposure when inhaled versus given subcutaneously". It is far from clear, however, how the company is going to fund development.

Splisense is also looking at this premature stop codon mechanism, though with an exon skipper. SPL23 induces skipping over exon 23 in the CFTR transcript, the company contends, bypassing the premature stop codon and allowing the production of active CFTR protein.

Tessera Therapeutics is working on something called Gene Writers: nucleic acids which, it claims, enable the correction of single nucleotides, the deletion or insertion of short DNA sequences, and the writing of exons or entire genes into the genome. In late 2021 the group signed an agreement with the Cystic Fibrosis Foundation to apply this technology to the disease.

In theory there is no reason why inhaled genetic medicines should not work in cystic fibrosis. But clinical data that are robust and convincing seem a very long way away.

| Inhale and hearty? Inhaled cystic fibrosis therapies in development | | | |
|---|---|---|---|
| **Product** | **Company** | **Mechanism** | **Status** |
| *Phase 2* | | | |
| 4D-710 | 4D Molecular Therapeutics | CFTR gene therapy (AAV vector) | Ph1/2 trial yielded data in 3 pts Nov 2022; enrolling a further 3-6 pts |
| SPL84 | Splisense | Antisense oligonucleotide | Ph1/2 trial in healthy volunteers and CF pts underway |
| *Phase 1* | | | |
| KB407 | Krystal Biotech | Redosable CFTR gene therapy (herpes simplex viral vector) | 2 Ph1 trials, in 13 and 20 pts, both could report 2024 |
| VX-522 | Vertex/Moderna | CFTR mRNA encapsulated by a lipid nanoparticle | Ph1 trial in 9 pts could report 2024; multiple dose study to start 2023 |
| *Preclinical* | | | |
| LUNAR-CF/ ARCT-032 | Arcturus Therapeutics | CFTR mRNA encapsulated by a lipid nanoparticle | Preclinical; positive data in ferrets reported Nov 2022 |
| SP-101 | Sumitovant (Sumitomo) | Single-dose gene therapy (AAV vector) | Preclinical; positive data in ferrets reported Nov 2022 |
| SP-102 (TL-102) | Sumitovant (Sumitomo) | Single-dose gene therapy (lentiviral vector) | Preclinical |
| Unnamed | Recode Therapeutics | CFTR mRNA encapsulated by a lipid nanoparticle | IND expected H2 2023 |
| ELX-02 Inhaled | Eloxx Pharmaceuticals | CFTR corrector | IND-enabling studies underway |
| SPL23 (EXON 23) | Splisense | CFTR exon 23 skipper | IND-enabling studies underway |
| BI 3720931 | Boehringer Ingelheim/ Oxford Biomedica | Redosable gene therapy (lentiviral vector) | Preclinical |
| Unnamed | Tessera Therapeutics | CFTR corrector | Preclinical |
| ARO-ENaC2 | Arrowhead Pharmaceuticals | ENaC RNAi therapeutic | Preclinical |
| *Note: CFTR=cystic fibrosis transmembrane conductance regulator; ENaC=epithelial sodium channel blocker. Source: Evaluate Pharma, company websites and releases.* | | | |