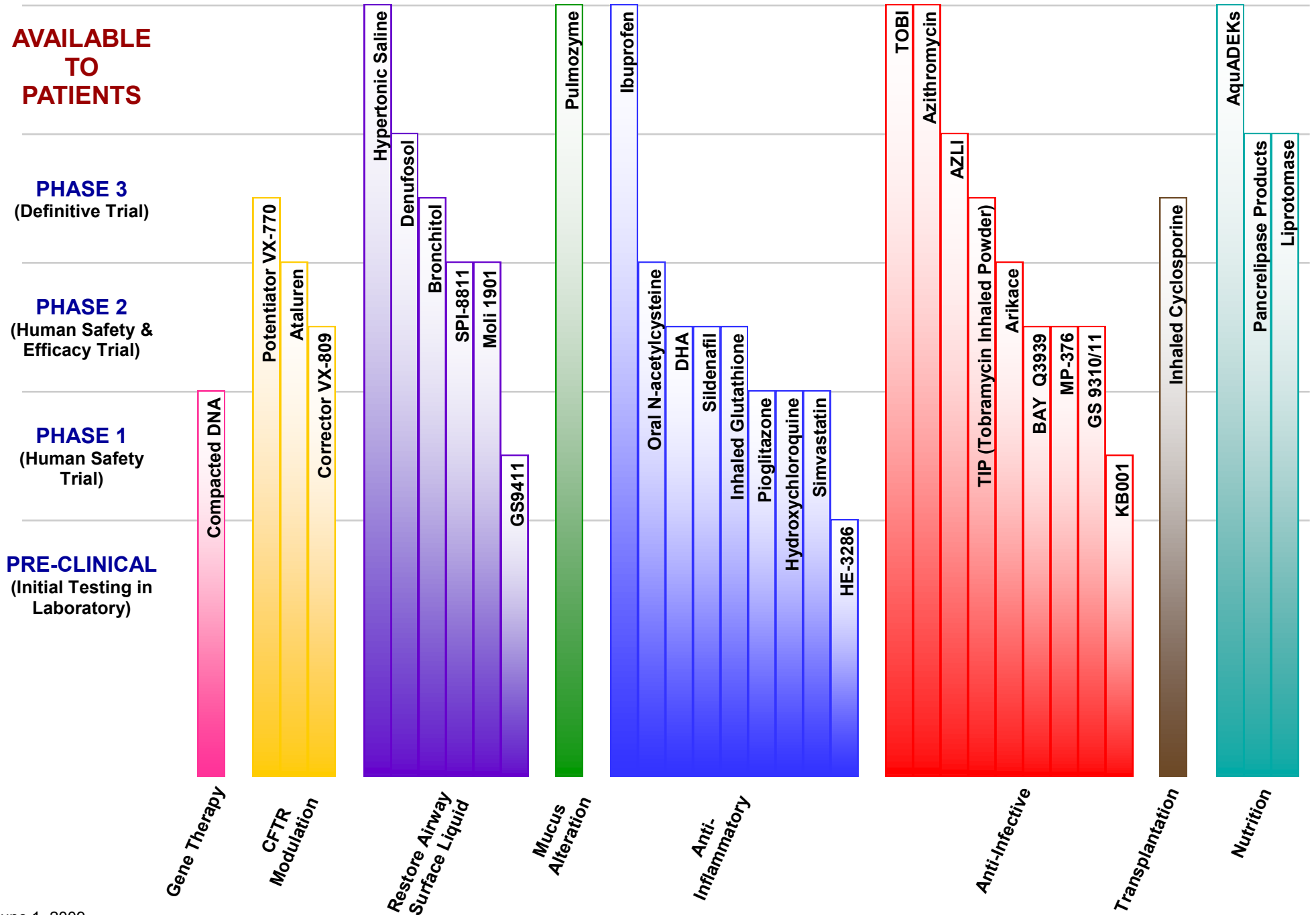


# Cystic Fibrosis Foundation Therapeutics Pipeline



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## ACRONYM KEY

CFF: Cystic Fibrosis Foundation

CFFT: Cystic Fibrosis Foundation Therapeutics, Inc.

CFTR: Cystic Fibrosis Transmembrane conductance Regulator

PA: Pseudomonas aeruginosa

TDA: Therapeutics Development Award

TDN: Therapeutics Development Network

## GENE THERAPY

- **Compacted DNA (PLASmin™)**: Copernicus Therapeutics, supported by a CFFT TDA and the TDN. Use compacted DNA (non-viral) to introduce normal copies of the gene into CF airways. A Phase 1a trial demonstrated chloride current changes in the noses of CF patients, but no evidence of gene expression. The gene therapy product is being reformulated prior to additional clinical trials in an attempt to improve the amount and duration of gene expression.

## CFTR MODULATION

- **VX-770**: Vertex Pharmaceuticals, supported by CFFT. VX-770 is a new compound called a "potentiator" that may act upon the CFTR protein and help to open the chloride channel in CF cells. Phase 1 dosing has been completed in healthy volunteers and CF patients. A Phase 2 trial in CF patients with at least one copy of a G551D mutation in their CF gene demonstrated improvements in biological measures of CFTR function (nasal potential difference and sweat chloride) and clinical measures of pulmonary health (FEV<sub>1</sub>). Two Phase 3 studies (one for pediatric and one for adolescent/adult patients) are scheduled to begin in spring, 2009.
- **Ataluren (formerly known as PTC124)**: PTC Therapeutics - A novel, small molecule compound, that promotes the read-through of premature truncation codons in the CFTR mRNA. It has been demonstrated to be safe, orally available and well tolerated in Phase 1 single dose trial in healthy volunteers. A Phase 2 trial in CF patients conducted in the U.S. and Israel demonstrated safety and encouraging biological results. A Phase 3 trial is scheduled to begin in summer, 2009.
- **VX-809**: Vertex Pharmaceuticals, supported by CFFT. VX-809 is a "corrector" that helps move defective CFTR protein to the proper place in the airway cell membrane and improve its function as a chloride channel. A Phase 2a trial began in spring, 2009.

## RESTORE AIRWAY SURFACE LIQUID

- **Hypertonic Saline**: A CFFT-funded, Phase 3 trial in Australia had beneficial effects on pulmonary health in CF patients. Follow-on studies are determining if younger patients would benefit from this inhaled therapy.
- **Denufosal**: Inspire Pharmaceuticals, supported by a CFFT TDA and the TDN. Correct the ion transport defect in CF. In June 2008, Inspire announced top-line results from TIGER-1, its first Phase 3 trial with denufosal for CF. The trial demonstrated statistical significance for its primary endpoint of change in FEV<sub>1</sub> from baseline compared to placebo. Inspire is currently enrolling patients in TIGER-2, the second pivotal Phase 3 trial with denufosal.
- **Bronchitol**: Pharmaxis - A Phase 3 trial of Bronchitol (an inhaled dry powder mannitol) has begun in the U.S. and Canada. Theoretically mannitol should help rehydrate CF secretions, improving airway clearance. Trials in Australia and Europe support this hypothesis.
- **SPI-8811**: Sucampo Pharmaceuticals and the TDN. Oral agent believed to bypass transport defect of chloride ions. Initial Phase 2a trial evaluating safety and efficacy. Thirty patients recruited.
- **Moli 1901**: Lantibio, supported by a CFFT TDA and the TDN. Thought to affect the ion transport defect in CF patients. Phase 1 trial demonstrated safety. Placebo-controlled, multi-dose, dose-ranging Phase 2 trial in Europe demonstrated positive changes in pulmonary function with highest dose.
- **Gilead GS9411**: A follow-on compound from Parion 552 that was used to demonstrate proof of concept, GS9411 has entered a Phase 1 CF clinical trial. Acts by blocking sodium absorption.

## MUCUS ALTERATION

- **Pulmozyme®**: Genentech, approved in 1993 and currently being used by more than 18,000 U.S. patients. Clinical trials were conducted in the CFF's care center network.

## ANTI-INFLAMMATORY

- **Ibuprofen**: A four-year CFF-supported high dose ibuprofen trial completed in 1990 demonstrated less lung function decline in the treatment group than the control group. This effect was greatest in 5-13 year-olds.
- **Oral N-acetylcysteine**: BioAdvantex - An antioxidant, oral N-acetylcysteine replenishes glutathione levels in neutrophils. Placebo-controlled 12-week study at Stanford Univ. demonstrated decreases in inflammatory cells in lung and positive indications of changes in pulmonary function.
- **DHA**: Univ. of Massachusetts, CFFT-supported as clinical research grant. Pilot study to examine effect of infant formula fortified with DHA on pathogenesis of CF in 120 newly diagnosed patients at 16 centers began in 2003.

June 1, 2009

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- **Sildenafil (Revatio):** Based upon prior work by researchers at University of New Mexico, clinicians there are examining whether sildenafil can lower markers of airway inflammation and measures of airway infection in CF patients as well as alter patient's perception of their own well being.
- **Inhaled Glutathione:** A Phase 1 trial of inhaled glutathione has been completed in Germany, and a Phase 2b trial is now in progress there.
- **Pioglitazone, Hydroxychloroquine:** These approved therapies (approved for non-CF indications) are being evaluated in exploratory Phase 1 trials in CF to determine if they are tolerated and if anti-inflammatory effects are seen.
- **Simvastatin (Zocor™):** A HMG-CoA reductase inhibitor that increases nitric oxide (NO) production in cultured CF epithelial cells. Investigators are evaluating, in a CFFT-funded trial, whether simvastatin increases exhaled NO production in CF patients, synthesis of pro-inflammatory cytokines and whether measures of inflammation in the upper respiratory tract correlate with those from the lower respiratory tract.
- **HE-3286:** Hollis-Eden Pharmaceuticals, supported by a CFFT TDA. An oral immune-regulating hormone which has replaced HE2000.

## ANTI-INFECTIVE

- **TOBI®:** Novartis Pharmaceuticals – This CFF/Children's Hospital, Seattle-developed aerosol antibiotic was licensed to Chiron and received FDA approval in 1997. Currently being used by more than 15,000 patients worldwide. Benefit at first sign(s) of *Pseudomonas* infection is being evaluated.
- **Azithromycin:** Pfizer – A large-scale, CFFT-conceived and supported, TDN-coordinated trial completed in 2002. In patients with chronic PA, this oral antibiotic improved lung function and weight gain, and decreased hospitalization rate. Two follow up studies are in progress.
- **AZLI:** Gilead Sciences, supported by a CFFT TDA and conducted in the TDN. Multiple Phase 3 trials of the aerosolized form of aztreonam, a widely used IV antibiotic in CF, have been completed and the FDA has reviewed all the data. Data from another clinical trial will be required but further discussions with the FDA are necessary to determine if ongoing trials will suffice.
- **TIP (Tobramycin Inhalation Powder):** Novartis Pharmaceuticals is developing Tobramycin as a powder to enable a faster, more convenient dosing regimen. Dosing of TIP will take a fraction of the time of liquid TOBI. A Phase 3 trial has completed enrollment.
- **Arikace™:** Transave – A liposomal formulation of the antibiotic amikacin. Animal model studies have shown it to decrease the PA burden in the lung. A Phase 1/2 trial in Europe has completed enrollment. A Phase 2 trial began in the TDN in 2007.
- **BAY Q3939:** Bayer Schering Pharma is developing an inhaled version of their antibiotic ciprofloxacin for treatment of airway infections. A small Phase 2 study in Germany is underway. A U.S. multicenter Phase 2 trial is currently enrolling patients.
- **MP-376:** MP-376 is a new formulation of levofloxacin being developed by Mpex Pharmaceuticals for aerosol administration to CF patients for management of chronic pulmonary infections due to *Pseudomonas aeruginosa* and other bacteria. A U.S. multicenter Phase 2 trial has completed enrollment.
- **KB001:** Kalobios Pharmaceuticals has initiated a Phase 1 clinical trial to test the safety of their antibody approach for treatment of *Pseudomonas aeruginosa* lung infections.
- **GS 9310/11:** Gilead Sciences inhaled combination antibiotic (fosfomycin and tobramycin) has completed Phase 1 testing in Australia. A U.S. multicenter Phase 2 trial is currently enrolling patients.

## TRANSPLANTATION

- **Inhaled Cyclosporine:** APT Pharmaceuticals – Inhaled formulation of cyclosporine was tested in a randomized placebo controlled trial at the Univ. of Pittsburgh. The group treated with inhaled cyclosporine showed a significant decrease in number of deaths and the development of chronic rejection. An additional clinical trial has been requested by the FDA before this drug is approved for clinical use.

## NUTRITION

- **AquADEKS:** Yasoo Health – Oral antioxidant vitamin formulation specifically for CF patients. A Phase 1 trial has been completed. A clinical trial to assess the safety and ability of this formulation to increase blood levels of antioxidants, normalize plasma levels of fat-soluble vitamins, improve pulmonary function and improve growth parameters began in 2007. AquADEKS is available to patients.
- **Pancrelipase Enzyme Products:** The FDA has required pancreatic enzyme products to be reformulated and undergo clinical testing in order to receive FDA approval. Companies completing this process include: Axcan Scandipharm (Ultrase), DCI (PANCRECARB), Eurand (Zentase), McNeil (Pancrease MT) and Solvay (Creon).
- **Liprotomase (formerly Trizyte):** Altus Pharmaceuticals, supported by a CFFT TDA, conducted in the TDN. Non-porcine pancreatic enzyme replacement. Phase 1 studies have not identified safety concerns. A Phase 2 trial has been completed, demonstrating safety and efficacy, and a Phase 3 trial has also been completed. Work to complete requirements for FDA submission is ongoing.