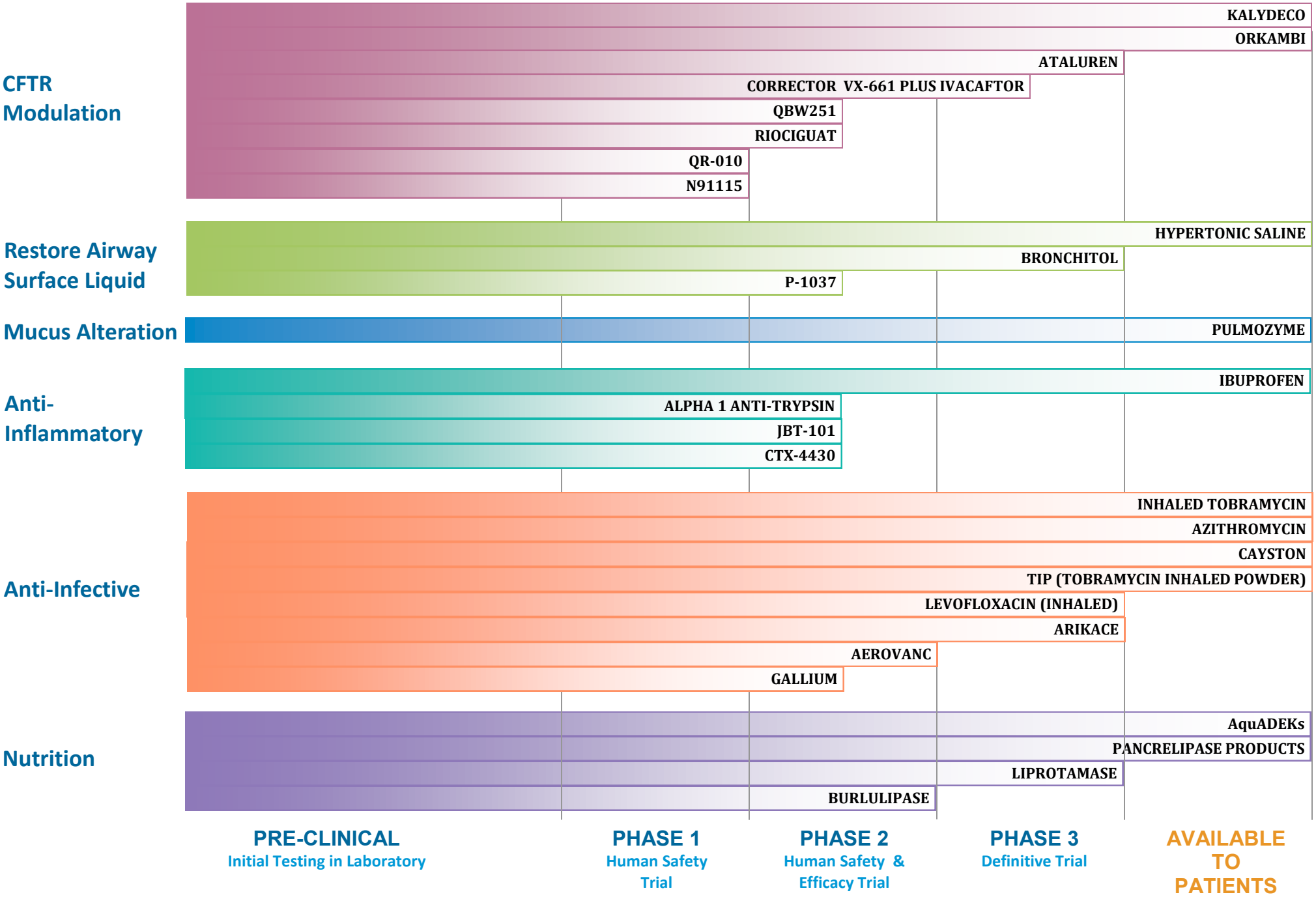
Cystic Fibrosis Foundation Therapeutics Pipeline



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The programs listed in the pipeline have received support from CFFT. This support may be either through research awards given directly to investigators /companies or through activities by the CFFT's TDN-CC. The TDN-CC facilitates programs through consultation, study management, and/ or protocol review by the expert review panel, the Protocol Review Committee. Most of the clinical trials for these therapeutic programs were conducted within the TDN.

ACRONYM KEY

CFF: Cystic Fibrosis Foundation **CFFT:** Cystic Fibrosis Foundation Therapeutics, Inc. **CFTR:** Cystic Fibrosis Transmembrane Conductance Regulator
TDN: Therapeutics Development Network **TDN-CC**: Therapeutic Development Network – Coordinating Center

CFTR MODULATION

- **Kalydeco™ (also known as ivacaftor):** The program is sponsored by Vertex Pharmaceuticals, Inc. and partially funded by CFFT. Kalydeco™ is a "potentiator" that targets the underlying cause of CF – a faulty gene and its protein product, CFTR. The FDA has approved the expanded use of Kalydeco™ for people with the following cystic fibrosis mutations: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P and G1349D and R117H.
- **Ataluren (formerly known as PTC124):** The program is sponsored by PTC Therapeutics and partially funded by CFFT. It is a novel, small molecule compound that promotes the read-through of premature truncation codons in the CFTR mRNA. These codons are due to what are known as "nonsense mutations". In 2011, a Phase 3 trial was completed in people with CF aged six and older, which showed that study participants who received Ataluren had a lower decline in lung function and a lower rate of pulmonary exacerbations, compared with those who took a placebo. Currently, a Phase 3 trial is recruiting people with CF who have nonsense mutations and are not taking aminoglycocides.
- **Orkambi™ (also known as lumacaftor and ivacaftor):** The program is sponsored by Vertex Pharmaceuticals, Inc. and partially funded by CFFT. Orkambi™ (formerly known as Lumacaftor plus ivacaftor) is a new therapy, combining a "corrector", designed to move defective CFTR protein to the proper place in the airway cell membrane, with the "potentiator" ivacaftor that improves function of CFTR as a chloride channel. The FDA has approved the use of Orkambi™ in people with CF who have two copies of the F508del CFTR mutation and are 12 years and older. A phase three trial is being conducted in children ages 6-11 who have two copies of the F508del CFTR mutation.
- **VX-661 plus Ivacaftor:** The program is sponsored by Vertex Pharmaceuticals, Inc. and partially funded by CFFT. VX-661 is a "corrector", designed to move defective CFTR protein to the proper place in the airway cell membrane and improve its function as a chloride channel. A Phase 2 trial for people with CF who have two copies of the F508del mutation was completed January. Several Phase 3 trials are being conducted in people who have one or two copies of the F508del CFTR mutation.
- **QBW251:** This program is sponsored by Novartis and facilitated by the TDN-CC. QBW251 is a type of CFTR Modulator called a "potentiator", similar to the drug ivacaftor, this drug would help to facilitate the opening of the chloride channel on the cell surface. This compound is administered through an oral pill. A phase 2 trial is currently underway.
- **Riociguat:** This program is sponsored by Bayer and facilitated by the TDN-CC. Riociguat is a novel therapy that stimulates sGC, an enzyme in the cardiopulmonary system and the receptor for nitric oxide (NO). Preclinical data has shown evidence that riociguat can result in improved CFTR channel expression. A Phase 2 trial is currently underway.
- **QR-010:** This program is sponsored by ProQR Therapeutics and partially funded by CFFT. QR-010 is an oligonucleotide designed to repair CFTR encoded mRNA, which could result in a wild-type or normal CFTR protein in people that have one or two copies of the F508del mutation. It is delivered via inhalation. QR-010 is designed to repair CFTR encoded RNA, which could result in a wild-type or normal CFTR protein. A Phase 1b trial will begin enrollment summer 2015.
- **N91115:** The program is sponsored by Nivalis, Inc. N91115 is a new oral compound that modulates the function of the defective CFTR protein and decreases inflammation in the lung. It is the first of a new class of compounds that increase levels of an important signaling molecule in the body, called S-nitrosoglutathione or GSNO. Levels of GSNO have been shown to be decreased in people with CF. These novel compounds have been shown to increase the amount of CFTR that reaches the cell membrane to stabilize CFTR so that its function can be improved. Currently, a multi-center Phase 1b trial is recruiting people with CF who have two copies of the F508del CFTR mutation.

RESTORE AIRWAY SURFACE LIQUID

- **Hypertonic Saline:** The program is fully funded through CFFT. Hypertonic saline as an inhaled therapy is believed to increase hydration of airway surface liquid in people with CF, thereby improving mucociliary clearance. A Phase 3 trial conducted in Australia had beneficial effects on pulmonary health in people with CF aged 6 years and older. A phase 2 trial of Hypertonic Saline in preschool children is currently underway. Hypertonic saline is currently being used by approximately 14,000 people in the U.S. with CF per the CFF Patient Registry.
- **Bronchitol**: The program is sponsored by Pharmaxis and facilitated by the TDN-CC. Bronchitol is an inhaled dry powder form of mannitol (an osmotic agent) that is thought to help rehydrate CF secretions, thereby improving airway clearance. A phase three trial of Bronchitol is currently underway in the U.S... It is approved for the treatment of CF in Australia and the UK. A New Drug Application has been submitted to the FDA.
- **P-1037:** This program is sponsored by Parion Sciences and partially funded by CFFT. P-1037 is a drug that blocks the sodium channel in airway cells and may prolong the duration that fluid in the airways can be maintained after hypertonic saline use, aiding mucus clearance. A phase 2 trial will begin enrollment Spring 2015.

MUCUS ALTERATION

- **Pulmozyme®:** The program was sponsored by Genentech, Inc. Pulmozyme® is an inhaled medication that thins and loosens mucus in the airway of people with CF. A Phase 3 clinical trial showed improvement in lung function and reduction in pulmonary exacerbations. It was approved for use by the FDA in 1993. Pulmozyme® is currently being used by more than 20,000 people in the U.S. with CF per the CFF Patient Registry.

ANTI-INFLAMMATORY

- **Ibuprofen:** The program was funded through CFF. Ibuprofen is an oral non-steroidal anti-inflammatory medication. A four-year high dose ibuprofen trial completed in 1994 demonstrated less lung function decline in the treatment group than the control group. The effect was more pronounced in people with CF who were less than 13 years old at time of entry. Ibuprofen is currently being used by approximately 500 people in the U.S. with CF per the CFF Patient Registry.
- **Alpha 1 Anti-Trypsin:** The program is sponsored by Grifols Therapeutics, Inc. Alpha 1 Anti-Trypsin is an aerosolized protease inhibitor with anti-inflammatory properties, derived from human plasma. A phase two trial was completed in the U.S. in 2013 and a second phase 2 trial will begin in January, 2015."
- **JBT-101:** This program is sponsored by Corbus and partially funded by the Cystic Fibrosis Foundation. JBT-101 (Resunab™) is an oral drug that may work by promoting the resolution of inflammation. It is thought to increase production of anti-inflammatory molecules while reducing production of molecules that increase inflammation. Reduction of inflammation may help stabilize lung function. A phase 2 trial will begin enrollment summer 2015.
- **CTX-4430:** This program is sponsored by Celtaxsys and partially funded by CFFT. CTX-4430 is an oral anti-inflammatory drug that reduces production of LTB4, a molecule that leads to inflammation and is known to be elevated in people with CF. Reduction of inflammation may help stabilize lung function. A phase 2 trial will begin enrollment summer 2015.

ANTI-INFECTIVE

- **Inhaled Tobramycin:** The TOBI ® program is sponsored by Novartis Pharmaceuticals (originally funded by the Cystic Fibrosis Foundation and Seattle Children's Hospital). The BETHKIS® program is sponsored by Cornerstone Therapeutics. TOBI® received approval by the FDA in 1997 and BETHKIS® received approval by the FDA in 2012. These drugs are an aerosolized form of the antibiotic tobramycin indicated to treat people with CF who are chronically infected with *Pseudomonas aeruginosa*.

- **Azithromycin:** The program is fully funded through CFFT and facilitated by the TDN-CC. Azithromycin is an oral antibiotic with reported anti-inflammatory properties. A Phase 3 trial showed CF patients with chronic *Pseudomonas aeruginosa* on azithromycin experienced improved lung function and weight gain, and decreased hospitalization rate. A follow-up trial showed that azithromycin decreased exacerbations in younger people with CF not infected with *Pseudomonas aeruginosa*. CFFT is supporting a trial in infants in Australia. Azithromycin is currently being used by approximately 12,000 people with CF in the U.S per the CFF Patient Registry.
- **Cayston®:** The program was sponsored by Gilead Sciences, Inc. and partially funded by CFFT. Cayston® is an inhaled form of the antibiotic aztreonam that received FDA approval in 2010 for people chronically infected with *Pseudomonas aeruginosa*. A Phase 3 clinical trial demonstrated improvement in lung function and respiratory symptoms. Additional trials have completed enrollment in people with CF who have mild disease and people with CF whose lungs are colonized with Burkholderia species. Cayston® is currently being used by approximately 6,000 people with CF in the U.S. per the CFF Patient Registry.
- **TIP (Tobramycin Inhalation Powder)**: The program is sponsored by Novartis Pharmaceuticals and was facilitated by the TDN-CC. TIP is an inhaled antibiotic, the powder form of tobramycin that may allow a faster, more convenient dosing. Based on Phase 3 trial results TIP received FDA approval in March 2013.
- **Levofloxacin (inhaled):** The program is sponsored by Rempex Pharmaceuticals, Inc. and facilitated by the TDN-CC.MP-376 is an inhaled formulation of the antibiotic, levofloxacin, for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* and other bacteria. A Phase 2b trial met the primary endpoint of *Pseudomonas aeruginosa* reduction in sputum and improvements in lung function were also demonstrated. The Phase 3 trial is complete.
- **Arikace™:** The program is sponsored by Insmed Incorporated and partially funded by CFFT. Arikace™ is an inhaled liposomal formulation of the antibiotic amikacin. A phase three trial in people with CF colonized with *Pseudomonas aeruginosa* was completed in Europe and Canada that showed improved lung function and reduction in *Pseudomonas* aeruginosa. A Phase 3 trial for the treatment of Nontuberculous Mycobacteria (NTM) is currently underway in the United States. Insmed announced lifting of clinical hold by *U.S. FDA on Arikace™ P*hase 3 trials in CF patients with *Pseudomonas aeruginosa* lung infections.
- **AeroVanc™:** This program is sponsored by Savara Pharmaceuticals and partially funded by CFFT. It is being conducted in the TDN. AeroVanc is an inhaled dry powder version of the antibiotic vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) airway infection in people with CF. Results from a U. S. multi-center Phase 2 trial showed that study participants who received AeroVanc experienced a significant reduction in MRSA density in their sputum compared to those given a placebo.
- **Gallium:** This program is sponsored by CFFT. Gallium is a molecule, nearly identical to iron, that disrupts iron-dependent biological processes and has been shown to kill antibiotic-resistant strains of P. aeruginosa in three different animal models. Gallium has already been approved by the FDA for intravenous use in humans and is now being tested in people with cystic fibrosis. A phase 2 trial will begin summer 2015.

NUTRITION

- **AquADEKs®:** The program is sponsored by Yasoo Health, Inc and partially funded by CFFT. AquaADEKs® is an oral antioxidant vitamin formulation specifically for people with CF. A clinical trial to assess 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 ended in 2008. Vitamin levels were significantly increased from baseline and inflammatory markers, including sputum neutrophils, were reduced. AquADEKs® is available to people with CF. A reformulation and additional clinical trials are ongoing.
- **Pancrelipase Enzyme Products:** The program is sponsored by Aptalis Pharmaceuticals (Zenpep®, Ultresa™ and Viokace™), Abbott (Creon®), Johnson and Johnson (Pancreaze®) and Digestive Care (Pertzye™). Digestive enzymes are prepared from porcine pancreases. The FDA has required pancreatic enzyme products to undergo clinical testing in order to receive FDA approval. Aptalis (Zenpep®), Abbott (Creon®), Johnson and Johnson (Pancreaze®) and Digestive Care (Pertzye™) have obtained FDA approval for their pancreatic enzyme products which are now available to people with CF.
- **Liprotamase (formerly Trizytek):** The program is sponsored by Lilly Pharmaceuticals and partially funded by CFFT. Liprotamase is a pancreatic enzyme replacement that is not prepared from animal sources. A Phase 3 trial has been completed. There were no safety concerns and the coefficient of fat absorption did improve. A Phase 3 trial will begin summer 2015.
- **Burlulipase:** This program is sponsored by Nordmark Pharmaceuticals and facilitated by the TDN-CC. Burlulipase is a liquid solution developed to treat pancreatic insufficiency due to cystic fibrosis. It is a bacterial lipase that has been shown to be more resistant against inactivation by gastric acid, giving it the potential to be more effective than the existing porcine pancreatin products. A phase two trial was recently completed in people with CF ages 12 and older.