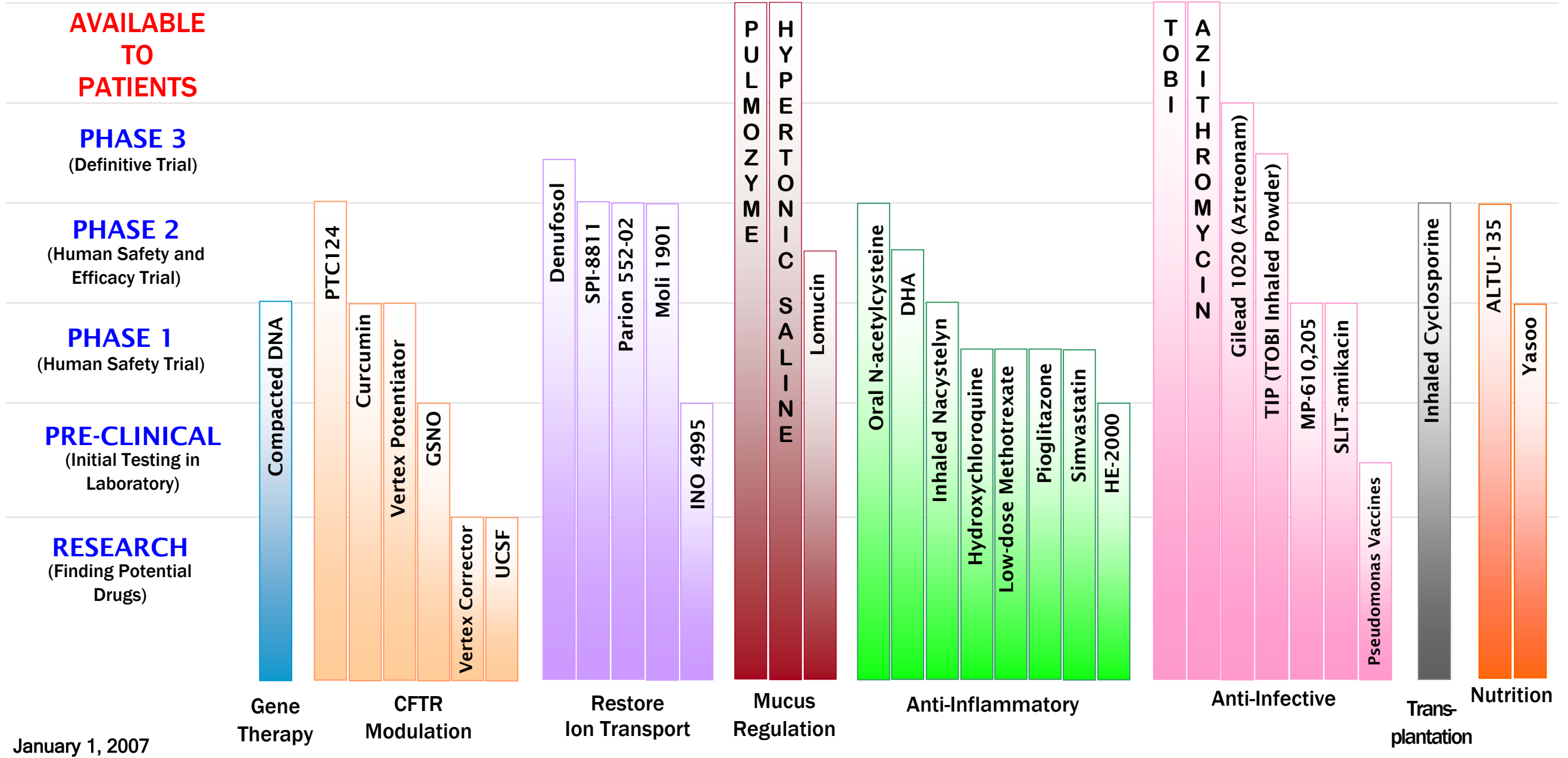


# CYSTIC FIBROSIS FOUNDATION THERAPEUTICS PIPELINE



January 1, 2007

#### 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

- **PTC 124** - 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.
- **Curcumin:** Seer Pharmaceuticals, supported by a CFFT TDA. Correct abnormal processing of CFTR in the cell. Curcumin appears to work in some strains of CF mice but not all. A previous Phase 1 trial in CF patients did not show correction of CFTR. A follow-on study at a higher dose is ongoing to confirm these findings.
- **VX-770:** Vertex Pharmaceuticals, supported by CFFT. VX-770 is a new compound called a "potentiator" that many act upon the CFTR protein and help to open the chloride channel in CF cells. Phase 1 dosing has been completed in patients. Researchers are evaluating results and Phase 2 could begin in early 2007.
- **GSNO:** Nitrox - S-Nitrosoglutathione (GSNO) levels are low in the lungs of CF patients. GSNO has been shown to promote trafficking of  $\Delta F508$  CFTR in some, but not all, tests on cultured cells. Nitrox LLC is developing inhaled GSNO for CF and is presently carrying out required preclinical safety studies as well as formulation studies.
- **CFTR Modulators including Correctors (Vertex and UCSF) and Potentiators (UCSF):** These are CFFT-supported, high-throughput screening programs that are in the research phase to identify correctors of the CFTR trafficking defect and additional potentiators of CFTR-mediated ion transport.

#### RESTORE ION TRANSPORT

- **Denufosal:** Inspire Pharmaceuticals, supported by a CFFT TDA and the TDN. Correct the ion transport defect in CF. Recently completed Phase 2 trial to determine the effect of drug on pulmonary function in CF patients demonstrated efficacy. A Phase 3 trial has begun.
- **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.
- **Parion** - Parion Sciences, supported by a CFFT TDA. Thought to correct the CF ion transport defects by acting primarily on abnormal sodium reabsorption. Phase 1 trials in normal volunteers and a single dose Phase I trial and a Phase II trial in CF patients are complete. Further plans are for an additional Phase II trial.
- **Moli** - 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 II trial in Europe demonstrated positive changes in pulmonary function with highest dose.
- **INO 4995:** Inologic, supported by a CFFT TDA, to be conducted in the TDN. Thought to correct the ion transport defect by acting on both the abnormal chloride and sodium transport. Preclinical testing is ongoing.

#### MUCUS REGULATION

- **Pulmozyme®:** Genentech, approved in 1994 and currently being used by more than 18,000 U.S. patients. Clinical trials were conducted in the CFF's care center network.
- **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.
- **Lomucin®:** Genaera Corp., with support from a CFFT TDA. A Phase 2a clinical trial conducted in Ireland did not reveal any safety concerns. A larger trial to assess efficacy began in 2005.

#### ANTI-INFLAMMATORY

- **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.

- **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.
- **Inhaled Nacystelyn:** Galephar Pharmaceutical Research, conducted in the TDN. Thought to act as a mucolytic and an anti-inflammatory. Phase 1 evaluation of safety and tolerability has been completed.
- **Hydroxychloroquine; Low-dose Methotrexate; Pioglitazone:** 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-2000:** Hollis-Eden Pharmaceuticals, supported by a CFFT TDA. An oral immune-regulating hormone is in preclinical testing.

### ANTI-INFECTIVE

- **TOBI<sup>®</sup>:** Novartis Pharmaceuticals – This CFF/Children’s Hospital, Seattle-developed aerosol antibiotic was licensed to Chiron and received FDA approval in 1998. Currently being used by more than 15,000 patients worldwide. Benefit at first sign(s) of Pseudomonas infection is being evaluated in a Phase 4 EPIC study which began in the 4<sup>th</sup> quarter of 2004.
- **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.
- **Aztreonam** - Gilead Sciences, supported by a CFFT TDA and conducted in the TDN. One Phase 3 trial is complete with several other Phase 3 studies of the aerosolized form of aztreonam, a widely used IV antibiotic in CF, ongoing; drug may be ready for market in 2007.
- **TIP (TOBI Inhaled Powder):** Novartis Pharmaceuticals – Developing TOBI as a powder to enable a faster, more convenient dosing regimen. Dosing of TIP will take a fraction of the time of liquid TOBI.
- **MP-610,205:** Mpex Pharmaceuticals, CFFT-supported. A bacterial efflux pump inhibitor that may increase the effectiveness of antibiotics in the treatment of chronic and acute bacterial respiratory infections in CF. A single-center Phase 1b clinical trial did not reveal safety concerns with the aerosolized product in CF patients.
- **SLIT-amikacin** - 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.
- **Pseudomonas Vaccines:** Several companies are in preclinical development of pseudomonas vaccines. The development of Berna Biotech's product, which was in Phase 2 testing, has been halted due to lack of efficacy.

### TRANSPLANTATION

- **Inhaled Cyclosporine:** Novartis 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

- **ALTU-135:** 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 is scheduled to begin in 2006.
- **Yasoo:** Yasoo Health – Oral antioxidant vitamin formulation specifically for CF patients. A Phase 1 trial has been completed.