Cystic fibrosis (CF) is the most common life-shortening genetic disease in the white population, affecting approximately 1 in 2500 live births (the carrier state for this autosomal recessive condition is about 1:25 in white people)**. In the State of Maine, there are currently approximately 250 children and adults with this disease.**

People with CF experience pulmonary complications resulting from the production of thick secretions in their lungs. All of the secretions cannot be cleared from their airways, which results in complications such as impaired gas exchange, bacterial infections and scar tissue formation. Bacterial infections cause exacerbations of the disease requiring inhaled antibiotics and intravenous antibiotic treatment. Each exacerbation causes further irreversible damage to the lung tissue, and progressive lung disease is currently the cause of death in approximately 85% of people with CF. To avoid these complications, affected individuals have traditionally required multiple sessions of aggressive daily airway clearance therapy, treatment with inhaled medications and increased nutritional support, all of which may require 2-4 hours per day (and more during an exacerbation).

In recent years biotechnology has transformed the treatment—and the lives—of most people with CF. A new class of medications called highly effective modulator therapy (HEMT) is now available for up to 90% of people with CF. These oral medication cocktails (developed through the screening of large compound libraries) are easy to take, improve lung function, reduce the frequency of hospitalizations and dramatically improve the quality of life of affected individuals. Early indicators point to marked improvement in life expectancy with these medications as well.

However, we are faced with a dilemma. Like all medications, HEMT is not a panacea for every person with CF. Approximately 10% of patients do not have genotypes responsive to HEMT. Others are not able to tolerate HEMT due to side effects. Furthermore, HEMT does not appear to reverse fixed injuries that develop early in life (such as male infertility and pancreatic insufficiency). Therefore, there is great interest among people in the CF community to look for more therapeutic options to address these gaps and shortcomings of HEMT.

Gene repair or replacement therapy, while still outside the scope of our current armamentarium, holds great promise as a strategy to treat people with CF disabled, for example, by nonsense mutations. More generally, treatment of genetic targets could change the trajectory of this disease with one-time ("one and done") or less frequent dosing starting at the earliest stages of life. **That would be the equivalent, in the minds of many, of changing the meaning of CF from "cystic fibrosis" to "cure found". Thus, there is great interest in the CF community to develop therapies (that is, gene-based, "mutation agnostic" therapies) that are effective for all people with the disease.**

A number of strategies (for example, RNA based treatments, DNA-based gene editing and gene replacement) are in relatively early stages of development and each carries a set of potential advantages and concerns, including durability of effect and whether benefits or harms could be passed along to offspring. However, we are right on the cusp of seeing such treatments for CF. Laying the groundwork for genetic therapies requires careful planning and preclinical testing, particularly for diseases like CF that for most can currently be in treated quite effectively. Perhaps more importantly, exploration of these novel therapies reveals important ethical and legal questions that entwine our humanity and that demand address by a cross section of society. For example, how do we intend to authorize and regulate *in utero* and/or germ cell line treatments for diseases that typically bring additional burden to daily living but do not lead to early childhood death? At this stage, a strong argument can be made to establish a

formal process by which interdisciplinary panels representing the spheres of religion, law, science, and public policy/public health review together information emerging from preclinical studies in advance of in-human trials.

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Research Experience and Potential Conflicts:

Grant Title: Gene therapy for CF (SCOR) Project III: Safety and efficacy of recombinant adenoviruses in the human lung
Funding Agency: National Institutes of Health
Period: 1997-99
Role: Principal Investigator

Grant Title: A phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in subjects aged 12 years and older with cystic fibrosis, homozygous for the *F508del-CFTR* mutation
Funding Agency: Vertex Pharmaceuticals, Inc.
Period: 2013-14
Role: Site, Principal Investigator

Grant Title: A phase 3, rollover study to evaluate the safety and efficacy of long term treatment with lumacaftor in combination with ivacaftor in subjects aged 12 years and older with cystic fibrosis, homozygous or heterozygous for the *F508del-CFTR* mutation
Funding Agency: Vertex Pharmaceuticals, Inc.
Period: 2014-16
Role: Site, Principal Investigator

Grant Title: A phase 2a, randomized, double-blind, placebo-controlled study to evaluate multiple doses of GLPG2222 in subjects with cystic fibrosis homozygous for the F508del mutation (FLAMINGO)
Funding Agency: Galapagos/AbbVie

Period: 2017-2018
Role: Site, Sub-Investigator

Grant Title: A Phase 1-2, randomized, double-blind, placebo-controlled, combined single and multiple ascending dose study evaluating the safety, tolerability, and biological activity of MRT5005 (CO-hCFTR mRNA/ICE LNP) administered by nebulization to adult subjects with cystic fibrosis (RESTORE-CF)
Funding Agency: Translate Bio MA, Inc.
Period: 2018-2021
Role: Site, Principal Investigator

Grant Title: A Phase 3, randomized, double-blind, controlled study evaluating the efficacy and safety of VX-121 combination therapy in subjects with cystic fibrosis who are homozygous for F508del, heterozygous for F508del and a gating (F/G) or residual function (F/RF) mutation, or have at least 1 other triple combination responsive *CFTR* mutation and no F508del mutation.
Funding Agency: Vertex Pharmaceuticals, Inc.
Period: 2021-present
Role: Site, Sub-investigator