



2010 Abstracts



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*Gene Therapy to Drive Endogenous
Biosynthesis of Prostacyclin*

The overall goal of this proposal is to design and test a gene therapy strategy for pulmonary arterial hypertension (PAH).

PAH is a rare, deadly, and incurable disease with a mean survival of 2.8 years from onset of symptoms, if left untreated. Of the three classes of approved therapeutics, endothelin receptor antagonists, phosphodiesterase inhibitors, and prostacyclins, prostacyclin is the most effective therapy. However, complicated delivery systems and potential side effects associated with the present formulation of prostanooids (e.g., prostacyclin) have deterred some patients and caregivers from instituting this highly effective class of agents. The challenge to be addressed by this proposal is the need for a therapeutic regimen that allows for endogenous production of prostacyclin therapy within the patient's own body, throughout the entire lifetime of the patient. Because prostacyclin can be produced endogenously through expression of the enzyme prostacyclin synthase (PGIS), gene therapy has previously shown proof-of-principle efficacy in animal models by enabling endogenous production of prostacyclin and reversal of experimental PAH. This proposal will build upon this concept, but will execute this strategy using newly developed gene transfer technology that obviates the viral gene delivery vectors used in prior studies. Viral vectors have been extremely useful in earlier studies, but



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have limited duration of expression, and, due to host immune response, cannot affect life-long therapy nor can they be re-dosed. Our gene delivery system, which uses ultrasound-induced microbubble cavitation to allow entry of non-viral DNA vectors into cells, is thought to evade host immune responses, theoretically allowing re-dosing of the PGIS therapeutic transgene as a periodic booster throughout the entire lifespan of the patient. An additional innovation of this proposal toward achieving the field-wide goal of endogenous prostacyclin production is the choice of the salivary glands as the therapeutic biosynthesis site. The salivary glands can be accessed through a bloodless, outpatient procedure, and contain a robust endocrine secretory pathway capable of secreting transgene products into the intravascular space. The encapsulated, fixed volume of the intraductal labyrinth of the salivary glands also allows precise control of the delivery system, making ultrasound-assisted gene transfer (UAGT) far more practical and consistent than has been observed in other organs (e.g., heart or pancreas). A final innovation of this proposal is the first in vivo application of a Cox-1/PGIS fusion protein that produces dramatically higher levels of prostacyclin than PGIS alone. In summary, this project seeks to innovatively test the enticing idea of PGIS-based gene therapy for PAH, aggregating three enabling technologies: 1) a practical, re-dosable gene delivery technique; 2) a novel biosynthesis site (salivary glands) that can be accessed through an outpatient procedure; and 3) a Cox-1/PGIS fusion protein transgene that produces superior levels of therapeutic prostacyclin. The efficacy of this gene therapy strategy will be tested in a highly relevant rat model of severe PAH.