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UNDERSTANDING TISSUE PHYSIOLOGY AS AN ESSENTIAL STEP TO ACHIEVING EFFECTIVE TISSUE-TARGETED GENE THERAPY

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In the mid-1960s a few visionary scientists suggested that one day it would be possible to transfer genes for therapeutic benefit. The tools of modern molecular biology allowed this vision to become reality, and already some patients have benefited enormously from gene therapy. However, equally important to this outcome was an understanding of the physiology of the cell types targeted for gene transfer. This latter requisite is often underappreciated amidst the glamour of genetic engineering, but it is absolutely fundamental to a successful gene therapy, as it is for any conventional therapy. My presentation will utilize our laboratory's experience in developing a salivary gland-directed gene therapy to illustrate this lesson.

We began using recombinant viral vectors for gene transfer to salivary glands ~15 years ago with a specific clinical goal; to correct the severe damage to these tissues following ionizing radiation (IR), received as part of the treatment for head and neck cancer. Each year ~35,000 patients develop such cancers in the USA, with ~500,000 cases worldwide. In industrialized countries, the treatment of most such patients includes IR. While the exact IR-induced damage mechanism remains enigmatic, fluid-secreting acinar cells are lost and salivary output is dramatically reduced. Since saliva plays a critical role in the physiology and protection of the upper gastrointestinal tract, and salivary exocrine proteins provide critical antimicrobial, lubricatory and reparative functions, these patients suffer considerable morbidity, including oral infections such as candidiasis and dental caries, mucositis, dysphagia, as well as frank discomfort. These morbidities result in a marked decline in a patient's quality of life. There is no conventional therapy for this condition, a circumstance frustrating to both patients and clinicians. Simplistically, in 1991 we viewed the major hurdle to achieving our goal to be gaining expertise with gene transfer vectors. We implicitly recognized that we had a reasonable "era-appropriate" understanding of the physiology of salivary glands, and thus could make a reasonable guess as to how to correct the pathophysiological condition. We hypothesized that increasing the water permeability of surviving relatively water-impermeable duct cells via a gene transfer procedure might be beneficial. Based on available evidence, we also reasoned that after IR duct cells could generate an osmotic gradient (lumen>interstitium) and, in the presence of a facilitated water permeability pathway, secretion of "a salivary fluid" could occur. Initially, we constructed a replication deficient, recombinant serotype 5 adenoviral vector designed to transfer the aquaporin-1 cDNA and began studies. In 2006 our hypotheses have proven to be generally correct, at least in rat and minipig models, and a clinical trial has been developed to assess the strategy in patients. While advances in molecular biology and virology certainly permitted successful gene transfer to occur, understanding the physiology of salivary glands allowed us to choose an appropriate gene for this novel therapy.