Scientific Abstract

Most patients with chronic wounds of the lower extremity fail to heal in a reasonable period of time. In fact, despite considerable advances in elucidating the molecular basis of wound repair, attempts at developing new therapies have been disappointing. In general, therapies based on recently elucidated mechanisms of wound repair have shown minimal improvement in the overall number of individuals with a treated healed chronic wound. In fact, in the few studies where cytokine growth factors have been efficacious, their effect has been dramatically less than would have been predicted from animal studies. The long-term goal of this project is to evaluate a new approach for healing venous leg ulcer and insensate diabetic foot ulcer, which are two distinct types of chronic wounds usually treated with medical therapy.

Current methods of applying cytokines to chronic wounds are inadequate. We hypothesize that a growth factor associated with wound healing PDGF-BB*, when produced in large quantities within the wound bed due to adenovirus mediated gene over-expression by the cells of the wound bed, will dramatically enhance wound healing. This study will use a unique and innovative gene therapy approach, adenovirus-Ad5 and the PDGF-B gene (called H5.020CMV*PDGF-B*), to insure delivery of a cytokine growth factor to a non-healing diabetic insensate foot ulcer. The growth factor, PDGF-BB, was selected because of its well established importance in wound healing and because preclinical studies using animal wound healing models have demonstrated the superiority of adenovirus mediated delivery of PDGF-B and ultimate production of PDGF-BB to traditional topical application of PDGF-BB for healing wounds. The adenovirus was selected because of its unique ability to efficiently and temporarily infect non-replicating cells. Simply stated, we plan to insure delivery of growth factor by using gene therapy techniques so that cells involved in the wound healing process locally and temporarily increase the production of PDGF-BB.

The aim of this study is to assess local and systemic toxicity in a dose escalation phase I trial, and the feasibility of using the maximum tolerated dose of H5.020CMV*PDGF-B* associated with *in vivo* PDGF-BB gene transduction via an intra-ulcer injection of H5.020CMV*PDGF-B* in patients with an insensate diabetic foot ulcer. Therefore, we will investigate the acute safety of this technique and its effect on two distinct chronic wounds, insensate diabetic foot ulcers and venous leg ulcer. This current study and future studies of other adenovirus mediated-growth factor combinations are collaborative efforts between investigators from the University of Pennsylvania Medical Center (Dermatology and Institute for Human Gene Therapy), the Wistar Institute, and the Children's Hospital of Philadelphia.

*Throughout this document, PDGF-B generally denotes the transgene and monomeric form whereas PDGF-BB represents the dimeric, active form of this growth factor.