Nu Skin Supports Stanford Dermatology Gene Therapy:
The Nu Skin Center for Dermatologic Research

Introduction

The Stanford University Department of Dermatology cutaneous research program aims to revolutionize the study and treatment of serious skin diseases. The ongoing research is making gains in the understanding and application of gene therapy and its potential to eliminate diseases that have long been considered incurable.

Gene Therapy at Stanford University

Over the past 25 years, Stanford scientists have made great strides in understanding the composition, structure, and expression of individual genes. They now know how to identify, manipulate, and replicate genes and can pinpoint genes associated with specific diseases. The potential of gene therapy to correct devastating diseases has not only revolutionized scientific research, but has created hope for complete and lasting cures.

In 1996, Dean Eugene Bauer, M.D., formed a medical school task force charged with advising him on the creation of a Program for Gene Therapy at Stanford. This task force strongly recommends that Stanford University School of Medicine initiate the Stanford Gene Therapy Program. The goal of this effort will be to bring together investigators from many disciplines throughout the university to focus on the translation of fundamental genetic discoveries into cutting edge patient care.

A New Center for Gene Therapy

Within the broader Stanford-wide gene therapy effort, Stanford researchers are poised to create the country s first center for cutaneous gene therapy to treat a diverse array of skin diseases. This center is a building block in Stanford s overall Gene Therapy Program, where genetic therapies would be adapted for a wide range of skin diseases. Scientists in the Nu Skin Center for Dermatologic Research will study single-gene-recessive and single-gene-dominant skin disorders, which are characterized by severe blistering, lack of skin adherence to the lower tissues, and excessive scaling, cracking and infection, as well as genetically complex skin diseases, such as psoriasis.

Research performed in the Nu Skin Center for Dermatologic Research would have a direct impact on patient treatment. Researchers in the Department of Dermatology are tackling problems that correspond to specific phases of clinical treatment, ranging from diagnosis to delivery of care. Research is structured in a vertically integrated fashion, with each project leading toward a comprehensive understanding and treatment of specific skin diseases. Genetic treatment of skin diseases will provide important insights into how gene therapy can be used to treat other diseases.

Epidermolysis Bullosa

Researchers in Stanford s Department of Dermatology initially are investigating how gene therapy can help people with epidermolysis bullosa (EB), one of the most severe inherited blistering disorders. This disease is characterized by genetic weakness of the skin, which causes skin to pull apart following minimal stress. Some children die within a year, while others live to be teenagers but suffer from deforming, painful, and lethal skin cancers. Successful genetic treatment of EB could lead to development or a standard approach to cutaneous gene therapy.

Stanford University School of Medicine is recognized as a leader in the study and treatment of people with EB. In 1988, it was designated as one of four regional clinical sites for the National Epidermolysis Bullosa Registry. The sites were established by the National Institutes of Health (NIH) to promote and facilitate further clinical and laboratory research in EB. 640 EB patients currently are enrolled in the clinical program at Stanford.

Advantages of Cutaneous Gene Therapy

Gene therapy is particularly well-suited to treating diseases of the skin, primarily because skin is highly accessible compared with internal organs. As a result, gene transfers, skin grafts, and biopsies pose minimal trauma and risk to the patient. Physicians can easily monitor and detect any adverse effects of newly introduced genes. Toxic effects on local tissue, for example, can readily be detected and affected cells removed without deep intervention.

Researchers hope to use gene therapy to treat systemic diseases by delivering therapeutic proteins through the skin to the rest of the body. Genes can be transferred directly into the skin or applied to patient cells in culture. Performing the transfer in culture allows scientists to ensure that the new gene is working correctly before the cells are re-administered to the patient.

Progress to Date

Stanford scientists have made significant strides toward using gene therapy in skin. Researchers routinely perform gene transfers in culture and have had initial success with transferring these cultured cells with corrected genes into living skin. They now know that it is possible to transfer new genes into the intact skin of a living patient.

Scientists face additional challenges in developing effective genetic treatments for skin diseases. Along with identifying the genes associated with specific skin disorders, they must also address problems such as difficulties in sustaining expression of therapeutic genes, regulation of therapeutic gene expression, and the potential for immune reactions to therapeutic gene products.

Researchers in Stanford s Department of Dermatology are leading the effort to make genetic therapy a reality for those suffering from serious skin diseases. The medical school s strength in the basic sciences, including molecular biology, biochemistry, cell biology, and immunology, combined with an outstanding clinical program, ensures a broad, multidisciplinary approach to the challenges of performing gene therapy. Researchers in the Department of Dermatology are participating in a NIH-funded project focusing on the molecular basis of EB. Cutaneous gene therapy is a logical extension of that project, and a natural next step in their investigation of this disease.

Faculty Projects

The effort to establish an effective gene therapy program for EB is divided into three major research projects led by a group of talented young investigators in the Department of Dermatology:

Dr. M. Peter Marinkovich, assistant professor, is focusing on four areas:

1) Identifying the structural defects in epidermolysis bullosa at the biochemical and cell biologic levels
2) Verifying the correction of the defects in EB cells and tissues to evaluate the effectiveness of gene therapy
3) Identification of novel basement membrane zone components which may be specifically affected in subsets of epidermolysis bullosa patients.

Dr. Paul A. Khavari, professor, is developing new gene delivery approaches to the skin. His group has recently succeeded in inserting genes in cutaneous stem cells and sustaining gene expression in human skin for prolonged periods. This advance has overcome the prior durability barrier and makes long-lasting genetic corrections feasible. Dr. Khavari s lab was the first in the world to achieve genetic correction of human skin disease tissue and he is extending these advances to develop a strong pre-clinical model of durable correction of human EB skin as a springboard for trial in humans.

Dr. Alexa Kimball assistant professor, is the director of clinical trials. She coordinates and directs the application of new therapies for patients. She maintains detailed methods to be certain that all clinical trials are done in an efficient, effective and safe manner.

The overall goal of these three projects is to develop effective approaches for sustained and reversible delivery of therapeutic genes to the skin as a foundation for gene therapy for EB.

Identifying New EB Proteins

Dr. Marinkovich s work allows him to identify new proteins in the extra-cellular matrix, or basement membrane zone of the skin that cause EB diseases. He uses monoclonal antibody technology to determine individual proteins roles in EB diseases. He and his colleagues have identified three novel matrix proteins, one of which has been shown to be defective in a subset of junctional EB patients. Dr. Marinkovich plans to continue the production of new monoclonal antibodies in an effort to identify additional novel proteins involved in human disease.

Controlling Gene Expression

Dr. Khavari is studying the problem of controlling the expression of delivered genes. He is developing methods to achieve sustainable and reversible gene delivery to the skin by, for example, finding a way to kill genetically engineered cells that produce undesirable results in the patient. He also is testing the effectiveness of direct gene delivery by transplanting engineered human skin tissue into immunodeficient mice. Dr. Khavari is using his findings to create a model for treating other skin and systemic diseases with gene therapy and as a platform for initiating the first gene therapy trial in humans. The goal is clear and the technology has been developed. Without adequate resources, however, the work cannot progress fast enough to help the thousands of children afflicted with EB and other severe inherited skin disorders.

Investment in the Future

Stanford University School of Medicine invites investment to bring new hope to patients suffering from the debilitating disease of EB. Gifts enable the Department of Dermatology to expand its gene therapy programs. Your support could help to launch the additional data needed to establish the effective gene therapy for EB and help us to develop the guidelines of this technology so it may be applied directly to patients with this severe blistering disease. Your contribution would be instrumental in funding a major advance in the use of gene therapy to treat inherited skin diseases and other serious afflictions.