Gene therapy of dominant epithelial genetic disorders by genetic modification of stem cells

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Genetic modification of stem cells opens entirely new perspectives for the treatment a variety of recessive and dominant genetic disorders of blood and epithelial cells. Genetic manipulation requires sophisticated tools to insert, or replace, genes into the human genome. For over two decades, vectors derived from retroviruses provided a simple and efficient tool to deliver, and integrate, genes into human stem cells for clinical application. Pioneer studies have demonstrated the potential of these vectors for the treatment of immunodeficiencies and skin diseases. A pilot clinical trial carried out by our group in 2006 showed that junctional epidermolysis bullosa, a skin adhesion disorder due to lack of laminin-5 at the level of the basal lamina, can be treated by transplantation of genetically corrected stem cells, leading to full phenotypic correction of the adhesion defect in affected patients. The successful outcome of this first clinical trial paves the road to gene therapy of other types of skin adhesion disorders. The different forms of epidermolysis bullosa affect approximately 500,000 people worldwide. Some of these diseases are of dominant nature, and require gene inactivation in addition to gene replacement technology. We are currently working on a pre-clinical gene therapy model of Meesman’s corneal dystrophy, a dominant disease caused by synthesis of mutated keratin 12 in the corneal epithelium. We propose a therapeutic strategy based on retroviral vectors synthesizing at the same time a shRNA against the mutated protein and an expression cassette for the wild-type protein. This type of technology could lead to restoration of normal cheratin 12 synthesis in the cornea, and serve as a model for all dominant disorder of the epithelia.