Clinical Potential of Hair-Follicle Derived Mesenchymal Cells in Cell Therapy: Multiple Therapeutic Applications

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INTRODUCTION

The hair follicle (HF) is a dynamic organ, which undergoes continuous morphogenesis and regeneration via the hair cycle throughout an animal's life. To support this unique characteristic of self-renewal, the HF retains reservoirs of multipotent cells. The dermal mesenchyme compartment of the HF comprises the dermal papilla (DP), a small aggregation cells at the base of the HF bulb; and dermal sheath (DS), which surrounds the bulb and envelops the HF. A specialized group of DS cells that localize at the base of the bulb and supports the growth of the DP is termed the dermal sheath cup (DSC) (Figure 1). Tissue engineering studies have demonstrated that DP and DSC cells play essential roles in hair development, growth and regeneration. Previously, we have demonstrated that cultured DSC cells can stimulate hair growth in mice, and our Phase I data show safety and efficacy in humans. Non-bulbar DS cells (NBDS), in comparison, do not possess HF inductive abilities, but do produce collagen. Exploiting the unique properties of HF cells, we have developed tissue-engineered cell-specific products containing autologous DSC cells or NBDS cells to treat various indications including androgenetic alopecia, tendinosis and aging skin.

OBJECTIVES

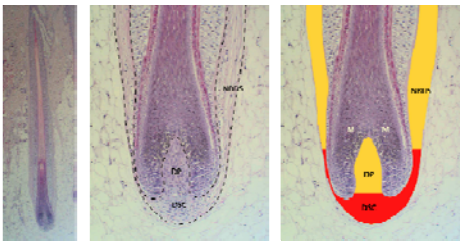
To assess preclinical safety and efficacy of cultured NBDS cells in treatment of tendinosis and aging skin.

METHODS AND RESULTS

NBDS cells were isolated from HF samples collected from three independent healthy subjects. Collagen production of NBDS cells in response to mechanical stress was analyzed by immunohistochemistry. Using immunodeficient mice and homologous rabbit models, biodistribution, tolerance and tumorigenicity of cultured human NBDS cells were examined in GLP-compliant *in vivo* studies.

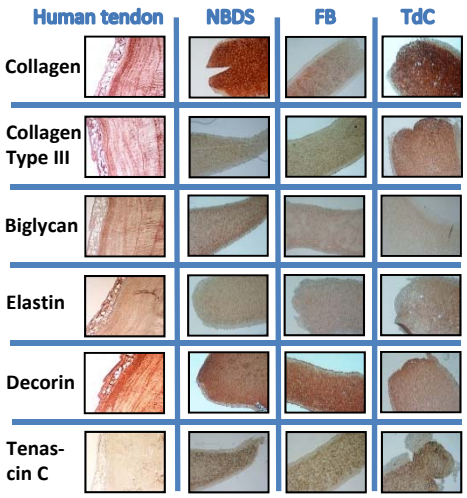
The results show that upon application of mechanical force, NBDS cells responded by producing type I collagen in the plane of the stretch and expressed other ECM-proteins including type III collagen and elastin. Our GLP-compliant *in vivo* studies showed that subcutaneously, or intratendon, injected NBDS cells were well tolerated, did not migrate to secondary sites and did not form tumours.

Figure 1. Schematic depiction of hair follicle cells



DP – dermal papilla
NBDS – non-bulbar dermal sheath
DSC – dermal sheath cup
M – hair follicle matrix cells

Figure 2. Tendon-related protein expression



Tendon-related protein expression was compared between plasma-embedded non-bulbar dermal sheath cells (NBDS), dermal fibroblasts (FB) and tendon cells (TdC) after 10-days of linear stretch.

Table 1. Summary of preclinical safety studies

Study Purpose	Local Tolerance	Tumorigenicity	Biodistribution
Objectives	To study tolerance of NBDS cells	To test potential of NBDS cells to form tumors	To study distribution of NBDS cells post-injection
Animal Model	New Zealand White Rabbits (6)	C.B-17 SCID-beige mice (40). Positive control: Hela adenocarcinoma cells	C.B-17 SCID-beige mice (30)
Injection Site	Intra-tendon: Achilles	Sub-cutaneous	Intradermal and sub-cutaneous
Duration	5 days	3 months	4 weeks
Analysis	observation and histopathology	observation and histopathology	RT-PCR
Results	No treatment related clinical abnormalities or mortality: mild reaction at local site in both placebo groups	No abnormal cell growth or tumor formation observed with NBDS cells	No detection of human cells in all organs and tissues examined

CONCLUSIONS

Our preclinical studies showed that cultured human NBDS cells express proteins essential in restoring healthy tendon and skin, and our *in vivo* studies confirmed safe application of human DS cells. A Phase I/II clinical trial using NBDS cells for the treatment of tendinosis in humans has been initiated.

CONFLICT OF INTEREST

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