Allogeneic fibroblast cell therapy for recessive dystrophic epidermolysis bullosa

Dr Gabriela Petrof
Clinical Research Fellow Genetic Skin Disease Group
St John's Institute of Dermatology
King’s College London, UK
Allogeneic fibroblast cell therapy for recessive dystrophic epidermolysis bullosa (RDEB)

• Basic problem in RDEB
• Pre-clinical mouse studies on fibroblast cell therapy
• Clinical studies leading to phase I and II clinical trials involving allogeneic fibroblasts.
• Set up, design and conduct of phase II clinical trial in the UK.
• Summary of what has been learned and future challenges.
What is the problem in RDEB?

RDEB is caused by mutations in the collagen 7 gene (COL7A1).
Mutations in the **COL7A1** gene lead to reduced type VII collagen (C7) and defective anchoring fibrils at the dermo-epidermal junction (DEJ).
Both keratinocytes and fibroblasts produce C7 with keratinocytes being the major source \textit{in vivo}.

Normal human keratinocytes in culture

Normal human fibroblasts in culture
What is the problem in RDEB?

Collagen VII at the dermo-epidermal junction of a healthy individual

Collagen VII at the dermo-epidermal junction of an RDEB individual

Normal human fibroblasts stained with collagen VII

RDEB fibroblasts stained with collagen VII
Pre-clinical studies of fibroblast cell therapy for RDEB

Gene corrected RDEB fibroblasts overexpressing C7 can produce correctly localised C7 at the DEJ

Injection of genetically engineered fibroblasts corrects regenerated human epidermolysis bullosa skin tissue

Susana Ortiz-Urda et al, J Clin Invest. 2003 January 15; 111(2): 251–255. doi: 10.1172/JCI200317193
Skin injected with gene-corrected fibroblasts

Skin injected with normal human fibroblasts

Skin injected with RDEB fibroblasts

Normal and gene-corrected dystrophic epidermolysis bullosa fibroblasts alone can produce type VII collagen at the basement membrane zone.

Pre-clinical studies of fibroblast cell therapy for RDEB
Long-term study on a mouse model of RDEB showing C7 expression at DEJ is increased for at least 100 days

Hypomorphic mouse expressing 10% C7 injected intradermally with

Hypomorphic fibroblasts
Normal human fibroblasts
Murine wild-type fibroblasts
No effect on C7

Pre-clinical studies of fibroblast cell therapy for RDEB

Intravenously injected normal or gene-corrected RDEB fibroblasts promote wound healing in mouse skin.

Intravenous injection of normal human or gene-corrected fibroblasts

Wounded site

Unwounded site

Intravenously Injected Human Fibroblasts Home to Skin Wounds, Deliver Type VII Collagen, and Promote Wound Healing
Clinical studies of fibroblast cell therapy for RDEB
First-in-human study of intradermal fibroblast injections for restoration of C7 at the DEJ

Single series of intradermal injections of human autologous and allogeneic fibroblasts on intact skin

Potential of Fibroblast Cell Therapy for Recessive Dystrophic Epidermolysis Bullosa
Tracy Wong et al., J Clin Invest, 2008 April 3, 28(9):2179-89, doi:10.1038/jid.2008.78
Clinical studies of fibroblast cell therapy for RDEB

A double-blinded randomised placebo-controlled trial of allogeneic fibroblasts in RDEB wounds demonstrated the safety of the technique (full study unpublished)

- Twelve patients screened and seven excluded. Five patients selected.
- Six pairs of symmetrical lesions in each patient received a single intradermal injection of GMP cultured allogeneic fibroblasts vs. transport solution (Transalyte with 2% Albumex).
- Followed up for 12 months with skin biopsies, blood tests, quality of life questionnaires and wound measurements.
- No benefit detected with allogeneic fibroblasts, but similar improvement described in both groups.

An open-label study of GMP-cultured allogeneic fibroblasts to RDEB wounds demonstrated clinical improvement in some individuals

- Fifteen patients with DEB received a single series of intradermal injections of GMP cultured allogeneic fibroblasts (Vavelta, Intercytex Ltd, UK).
A phase II clinical trial of allogeneic fibroblast cell therapy for RDEB - design

- Randomised, double-blinded, placebo controlled, phase II clinical trial.
- Individuals with RDEB with more than 5 chronic wounds.
- Single series of intradermal injections of allogeneic fibroblasts around wound margins.
- Follow-up with serial photography, wound measurements and quality of life assessments.
Takes a small army to run a study: Communication is the key

- Sponsor
- Principal Investigator
- Operational team
  - Project Manager
  - Database Manager
  - Statistician
  - Monitor
- Enrolling site team (research doctor and nurse)
- Drug manufacturing team
Trial roadmap
Regulatory approvals

- Ethics Committee approval
- Medicines and Health Authority (MHRA) approval
- Clinical Research Facility panel approval may/may not be needed
- R&D approval
- Protocol amendment (minor or substantial)
- Adverse event reporting
- Monitoring
Study timeline

Screening visit
- Day 7
- Day 28
- Week 12

D0- Injection day
- Day 14
- Day 56
- Week 24
A phase II clinical trial of allogeneic fibroblast cell therapy for RDEB – study drug and conduct

- Unrelated neonatal foreskin
- Primary fibroblast cell isolation from skin biopsy
- Allogeneic fibroblast suspension
- Intradermal injection around the wound margins
A phase II clinical trial of allogeneic fibroblast cell therapy for RDEB - Methods

The wound photo is uploaded.

Calibration and mapping of the wound edge follows.

Analysis of the wound surface area and tissue.
Summary

• Intradermal injections of allogeneic fibroblasts have proven safe at a clinical level.
• They can ameliorate the blistering tendency in people living with RDEB.
• They may benefit wound healing in mild to moderate cases.
• Further work is needed to study the mechanism of action of dermal fibroblasts in promoting formation of new C7.
• Determine the optimal clinical application of fibroblast or other cell types (e.g. Bone marrow-derived mesenchymal stromal cells).
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