

DEBRA International's Research Programme in Epidermolysis Bullosa



DEBRA's mission '*working for a life free of pain*' embraces not only action to deliver care, but also research to develop improved treatments.

Progress in developing therapies

With recent research developments, there are several therapeutic approaches which may be useful in treating the genetic defects in EB, and are being developed by DEBRA-funded researchers and others.

Translating research into the clinic will provide:

- More accurate diagnoses
- New diagnostic tests
- More specific treatments
- Better clinical management
- Therapies that prevent disease or decrease symptoms

EB is caused by defects in one or more of the proteins that make up the skin. These proteins are defective because the genes that code for the proteins have mistakes in the code.

- 3 major types of EB
- 10 genes, which encode skin proteins
 - keratins 14 and 5, plectin (EBS)
 - collagen VII (RDEB and DDEB)
 - laminins, integrins, collagen XVII (JEB).

To cure EB, we must therefore introduce into the skin either enough of the correct form of the protein which is faulty (protein therapy), or the correct form of the gene that can make that protein (gene therapy), or enough cells containing the correct gene (cell therapy).

Different types of therapies are being developed, all of which have advantages and disadvantages.

Protein therapy

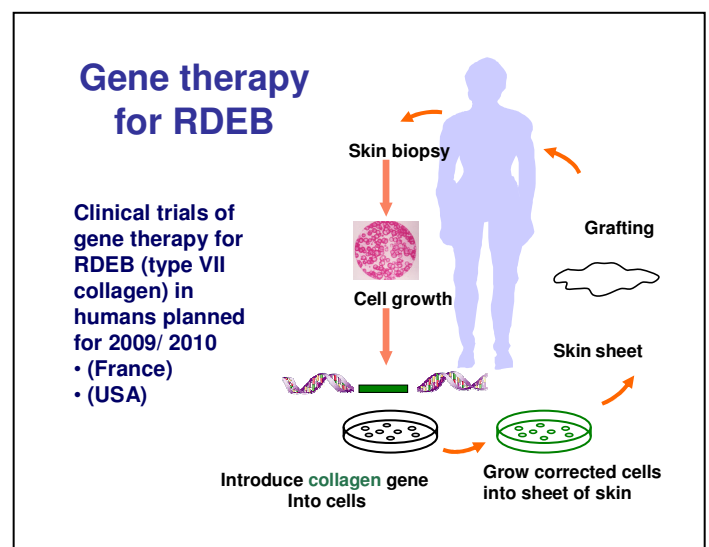
Aims to strengthen skin locally by injection of enough of the correct form of the protein that is missing or defective in someone with EB

- Correction of RDEB blistering in mice by injections of collagen VII protein healed wounds and prevented blistering.
- **A Phase I clinical trial of collagen protein therapy in humans is planned for 2010**

Ex-vivo Gene Therapy

Aims to strengthen skin locally by grafting skin which is genetically corrected

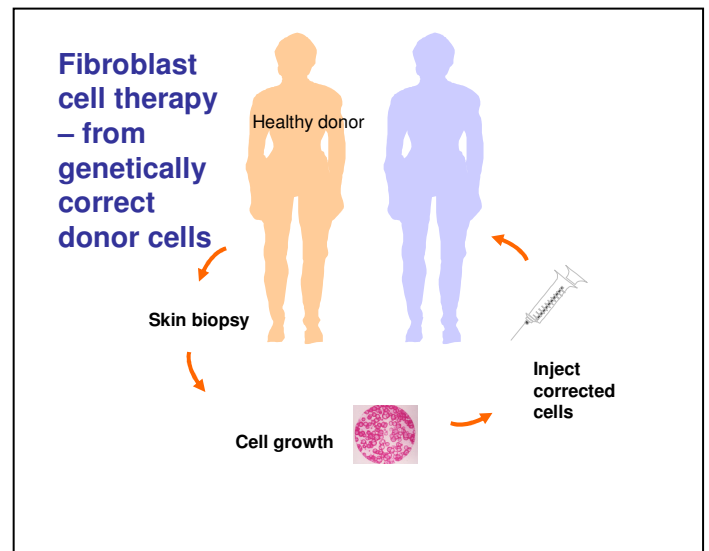
- First successful 'proof-of-principle' of a gene therapy for a type of EB (JEB) reported in 2006
- Grafted a patch of patient's own skin after correcting it in laboratory by introducing missing gene.
- 3 years after grafting the gene-corrected skin, the transgene is still being expressed and an increased amount of functional laminin 332 is present in the skin
- **Clinical trials of gene therapy for RDEB (type VII collagen) in humans planned for 2009/ 2010**
 - **Hovnanian et al (France)**
 - **Lane et al. (USA)**



Fibroblast cell therapy

Aims to strengthen skin locally by injecting healthy-donor fibroblast skin cells into RDEB patient's skin

- Fibroblasts can make enough collagen to glue epidermis to dermis
- Injection of fibroblasts from donors around EB wounds improves local healing of wounds temporarily (for several months)
- Therapy derived from work by McGrath research group, Guy's & KCL, DEBRA fellowship)
- Collaboration with company who has donated fibroblasts allowed 13 patients to be treated in pilot trial: all patients showed improved healing, reduced blistering, with no side effects.
- **A Phase II trial of fibroblast therapy is planned for 2009/ 2010**



Chimeric skin-equivalent grafts

- Can also make 'hybrid' skin grafts using donor fibroblasts and patient keratinocytes
- Fibroblasts less immunogenic than keratinocytes
- Therapy derived from collaboration between Biomedical company and Spanish EB research group
- 2006: chimeric skin equivalent granted orphan drug status for EB treatment by European Medicines Agency (EMA)
- **Phase IIb clinical trial ongoing**

Local versus Systemic Therapies

Grafting, and therapies using intradermal (i.e. into the skin) injection of protein or cells, are **local therapies**. These can make a big difference to help chronic wounds heal and strengthen skin locally, But...ideally...we would like to develop **systemic (i.e. whole-body) therapies** to treat all sites (internally too).

Cell therapies are a temporary cure, unless they are stem cells

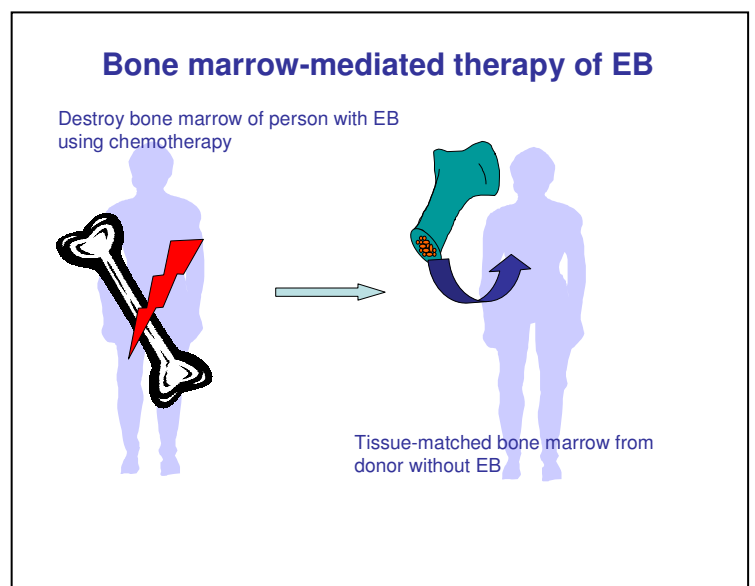
Even where fibroblast skin cells used in cell therapies are closely matched between donor and EB patient, the injected cells will eventually die – unless they are stem cells. In both normal skin and EB skin, new skin cells are derived from skin stem cells.

- Bone marrow cells are 'stem cells' which can reproduce themselves indefinitely.
- Bone marrow cells can therefore be used to develop a long-term renewable 'stem cell' supply of new skin cells

Bone-marrow stem-cell therapies

Aims to strengthen skin systemically by providing donor bone-marrow stem cells which provide the recipient patient a lifelong supply of genetically correct skin stem cells

- A possible 'cure'?
- A bone marrow transplant in an RDEB patient should give fewer blisters, and more collagen VII appears in skin.
- BM transplant is an established medical procedure but still very risky
- Not known which cells from bone marrow have beneficial effect
- Not known whether benefits will be short-term or long-term
- Further research needed



In RDEB patients:

- **University of Minnesota BMT trial ongoing (results not yet published)**
- **Five patients treated (two died).**
- **Follow-up on one patient for 434 days shows clinical improvement: stronger skin, and fewer blisters.**
- **University of Columbia (NY) clinical trial with less severe chemotherapy protocol - may be better tolerated**

Inducible pluripotent stem cells

Aims to provide a new source of genetically corrected stem cells by reprogramming the patient's own skin cells to become embryonic-like stem cells

- Reprogramming requires insertion of four additional genes, as well as correcting EB gene fault
- Has advantages of embryonic stem cells, without ethical dilemmas
- Early-stage research technology – risks not yet fully known
- **DEBRA Austria has just funded a new research group to develop technology specifically for EB**

Drug therapies

Aims to strengthen skin systemically by altering patterns of gene expression.

Two examples in development so far:

(1) 'Knockout and replacement' siRNA therapy for EB Simplex

- Knockout expression of faulty keratin gene with 'siRNA' (small molecules – pharmaceutical type drug)
- If necessary, increase activity of a replacement gene
- 'Knockout and replacement' works in mice
- DEBRA funds a 5-year programme 'RNA Therapeutics for EBS' (in Scotland)
- Major progress in developing mechanisms for switching off faulty keratin genes in EBS, and developing 'replacement' keratin genes.
- A gene therapy system with the potential to treat EBS patients carrying a keratin 14 mutation has now been successfully tested in skin cells in the laboratory
- **Early-stage trial for EBS patients currently being designed**
- **Technology also applicable to DDEB**

(2) Preventing premature termination of gene expression

- Some genetic faults in EB cause the skin cell's protein-making machinery to stop working before the protein is complete
- Some drugs e.g. PTC124, or gentamicin, prevent the protein-making machinery from recognizing the premature stop signal, so a normal length protein is made
- **Early stage work, that will only apply to some specific mutations, but could be effective for those patients**

...Future challenges for DEBRA

- To date, research and delivery of care have been largely separate - but this will change with the development of a range of treatments and possible cures.
- DEBRA now faces the challenge of prioritizing its support activities to get potential therapies evaluated and approved for clinical use as rapidly and efficiently as possible
- The cost of taking research from lab to clinic increases at each stage of the process: recent European legislation will significantly increase the cost and time required to gain approval
- We will need to raise additional funds (perhaps 10-50-fold more).
- We may need to consider new ways of working so that additional funding can be raised and experience of taking research through regulatory approval into the clinic gained (e.g. cooperation with industry).
- DEBRA needs now to consider and plan how it can help EB patients to participate in clinical trials, and to access approved therapies and improved treatments.

For further information on DEBRA Research, go to: <http://www.debra-international.org/research/>