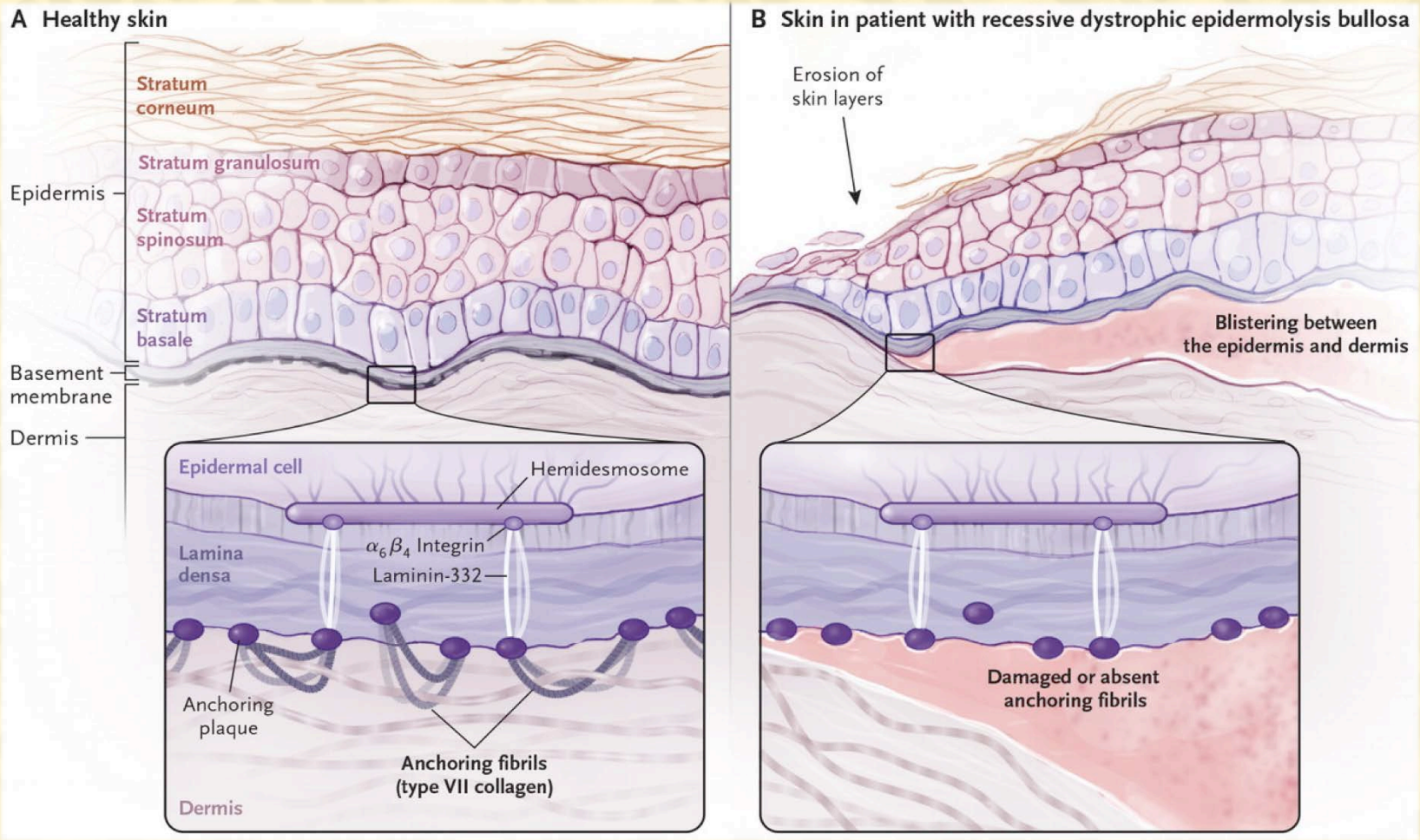
BMT for RDEB and JEB

What have we learned, and what do we do next?



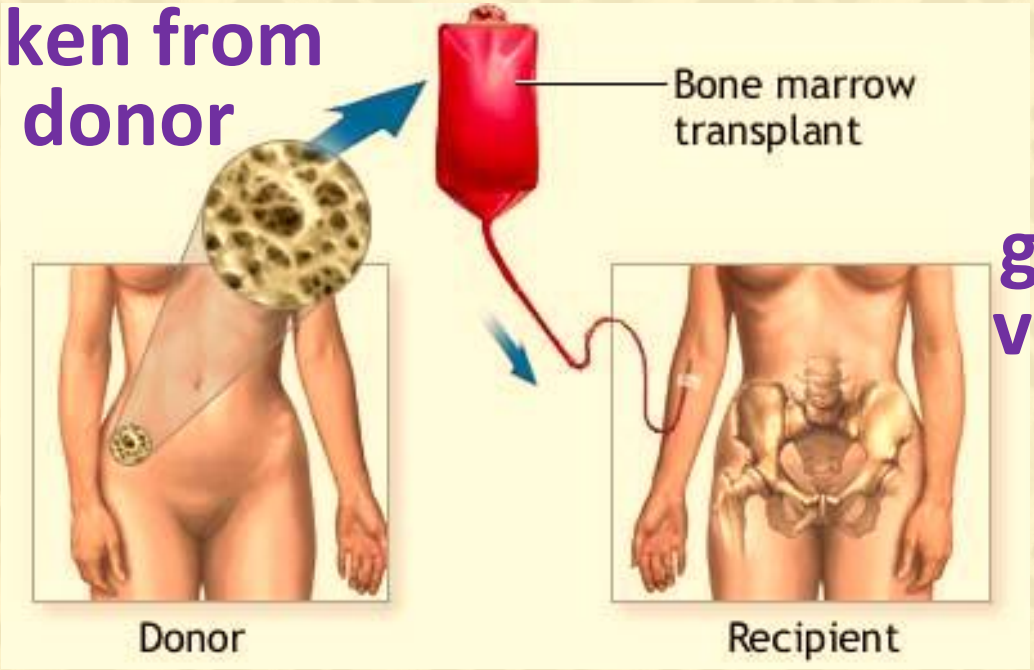
NEJM 2015

Jakub Tolar MD PhD
University of Minnesota

How does BMT work in EB?

Hypothesis

Blood-producing stem cells taken from donor

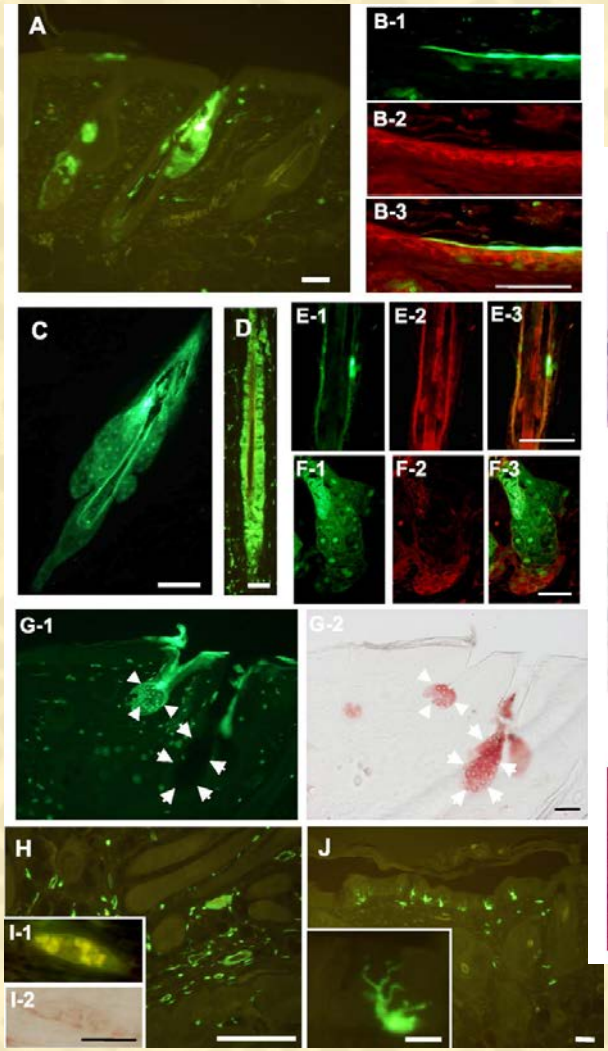


Donated cells given to patient via bloodstream

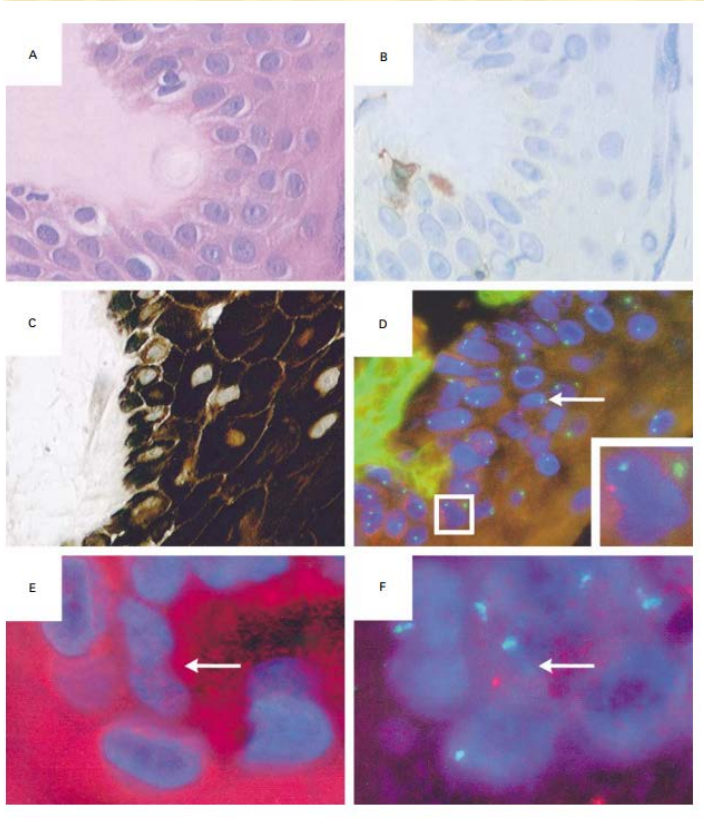
Donated cells circulate through the recipient's body and produce missing collagen

Donated cells engraft in bone marrow and produce healthy cells

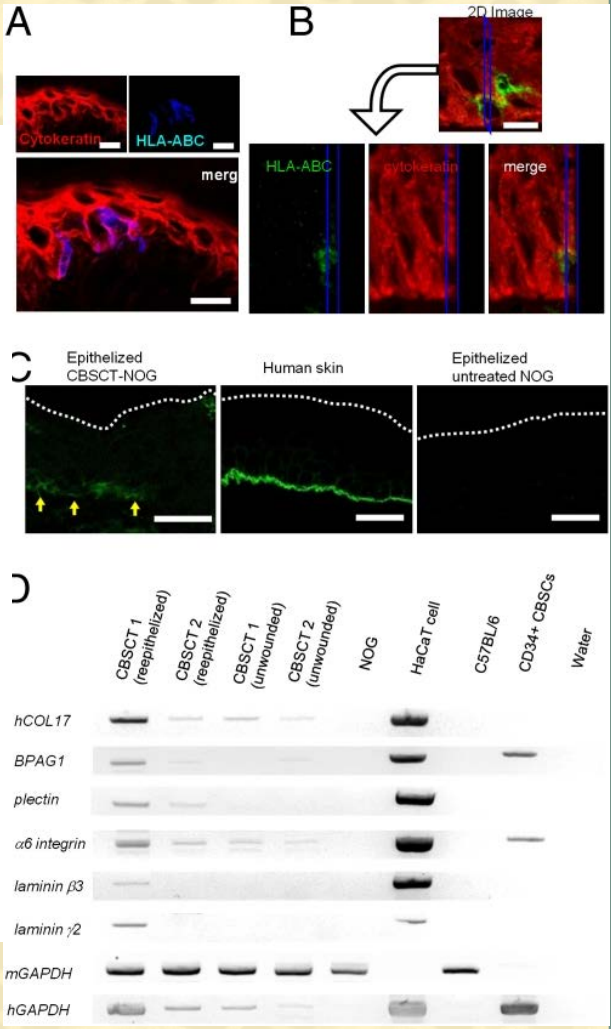
Do bone marrow cells engraft in skin?



Kataoka *Am J Pathol* 2003

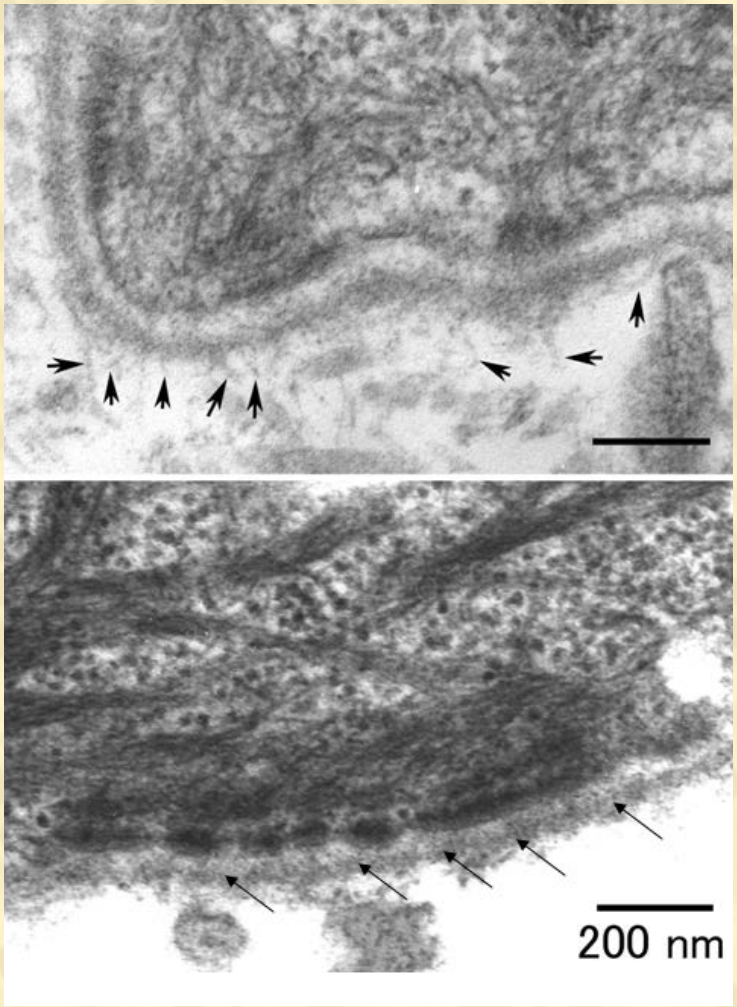


Körbling *NEJM* 2002



Fujita *PNAS* 2010

Does BMT work in EB?



Blood 2009

Should we do BMT for EB?

Systemic impacts of EB

- Internal surfaces
- Pain
- Itch
- Fibrosis
- Anemia
- Malnutrition
- Autoimmunity
- Dentition
- Kidney
- Heart

Is BMT reasonably safe?

- UMN Institutional Review Board
- External review boards

Protocol and patient safety

Colleen Delaney, MD

Gay Crooks, MD

Patient review

John McGrath, MD

Alain Hovnanian, MD

Hiroshi Shimizu, MD, PhD

Katsuto Tamai, MD, PhD

How do we do BMT for EB?

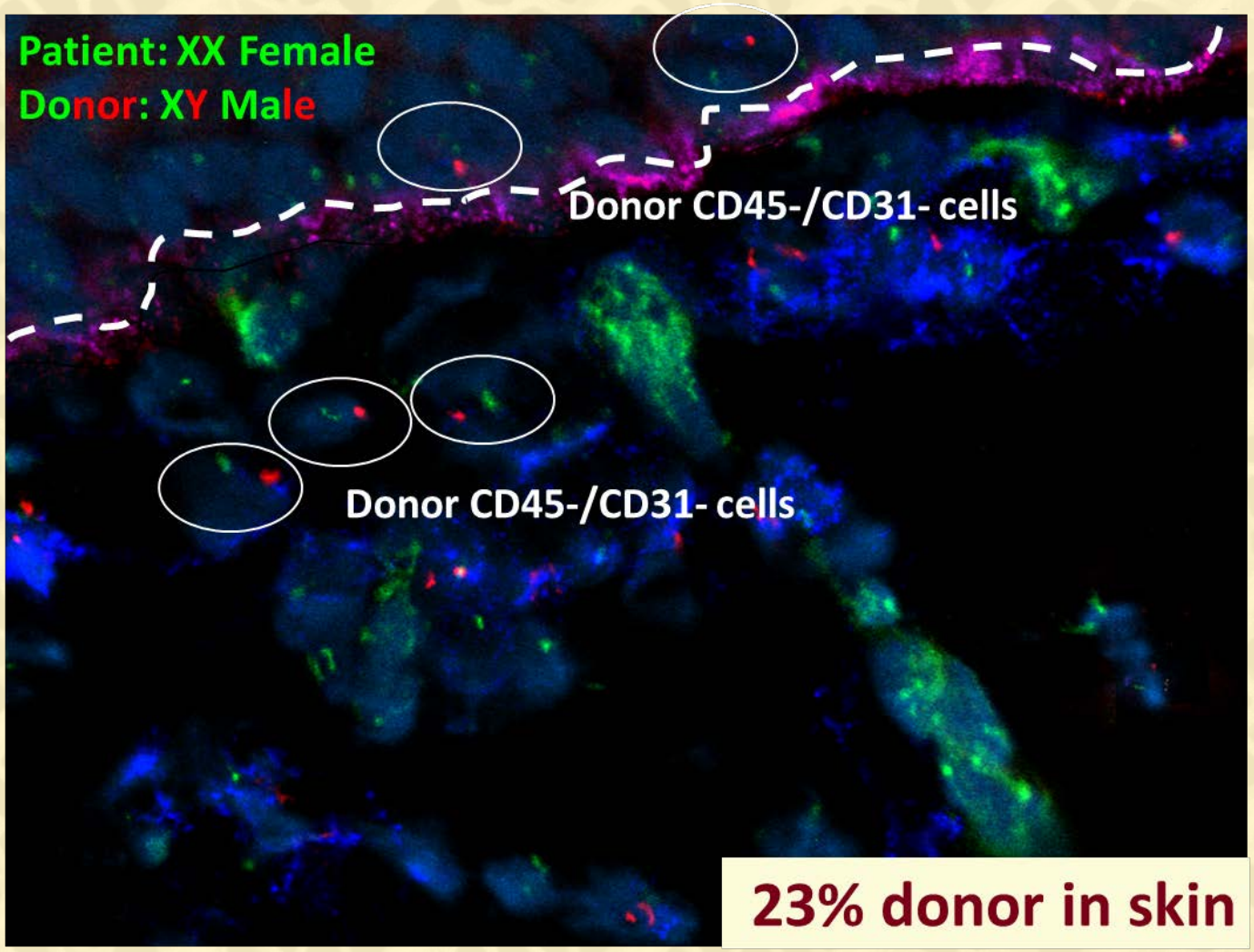
Adaptive Clinical Trial – 2007 to present
Safety & effectiveness

- **FDA Investigational New Drug IND 14166**
- **Clinical Trials (clinicaltrials.gov):**
  - BMT for Severe EB (high dose): NCT00478244 - closed
  - MSCs for Severe EB: NCT02581775
  - Skin grafting – using BMT donor skin: NCT02670837
  - BMT for Severe EB (low dose/haplo donor): NCT0103355

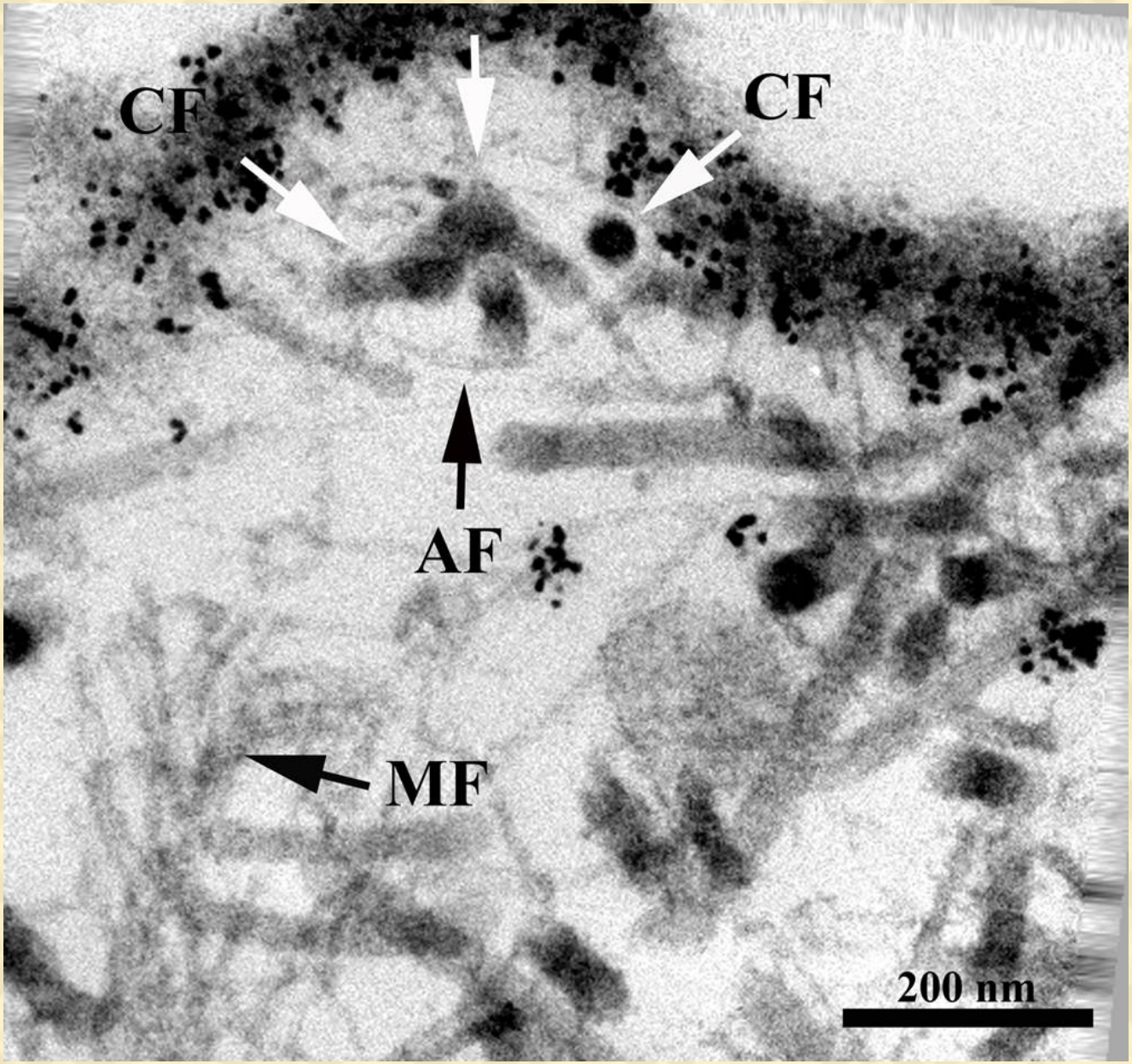
How do we know if it works?

Multiple measurements made at set timepoints:

Engraftment: presence of donor cells in patient's skin



How do we know if it works?

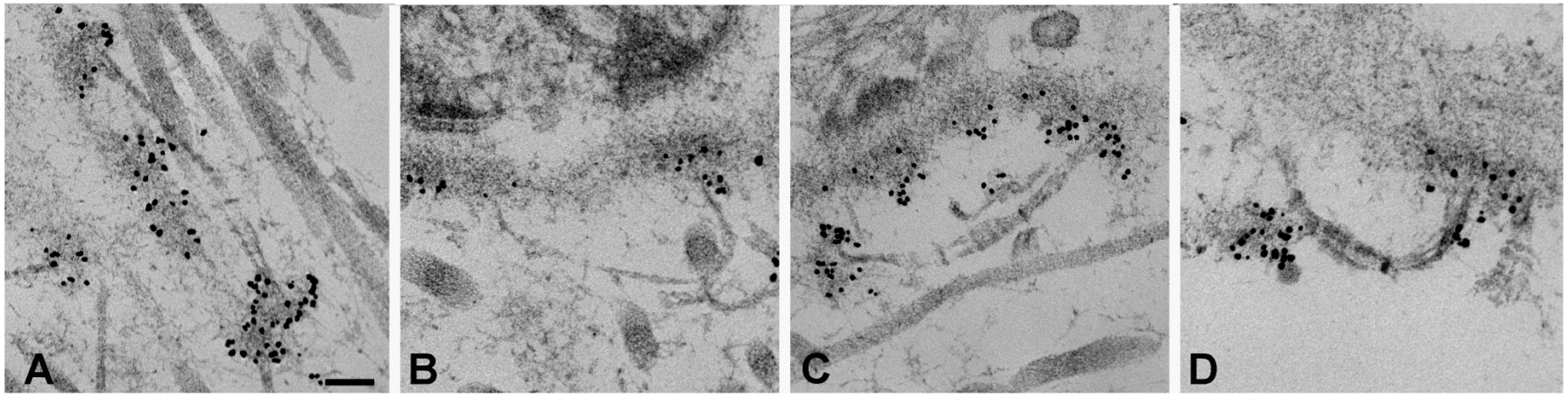


Visual and antibody identification of anchoring fibrils (electron microscopy)

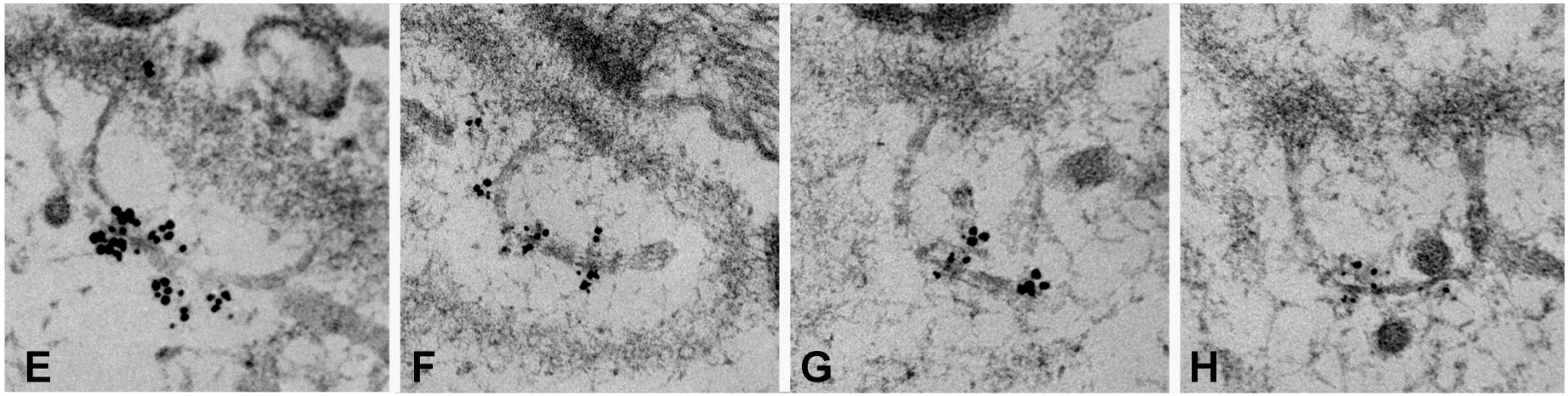
How do we know if it works?

Persistence: anchoring fibrils: 7 years after BMT

mAb185

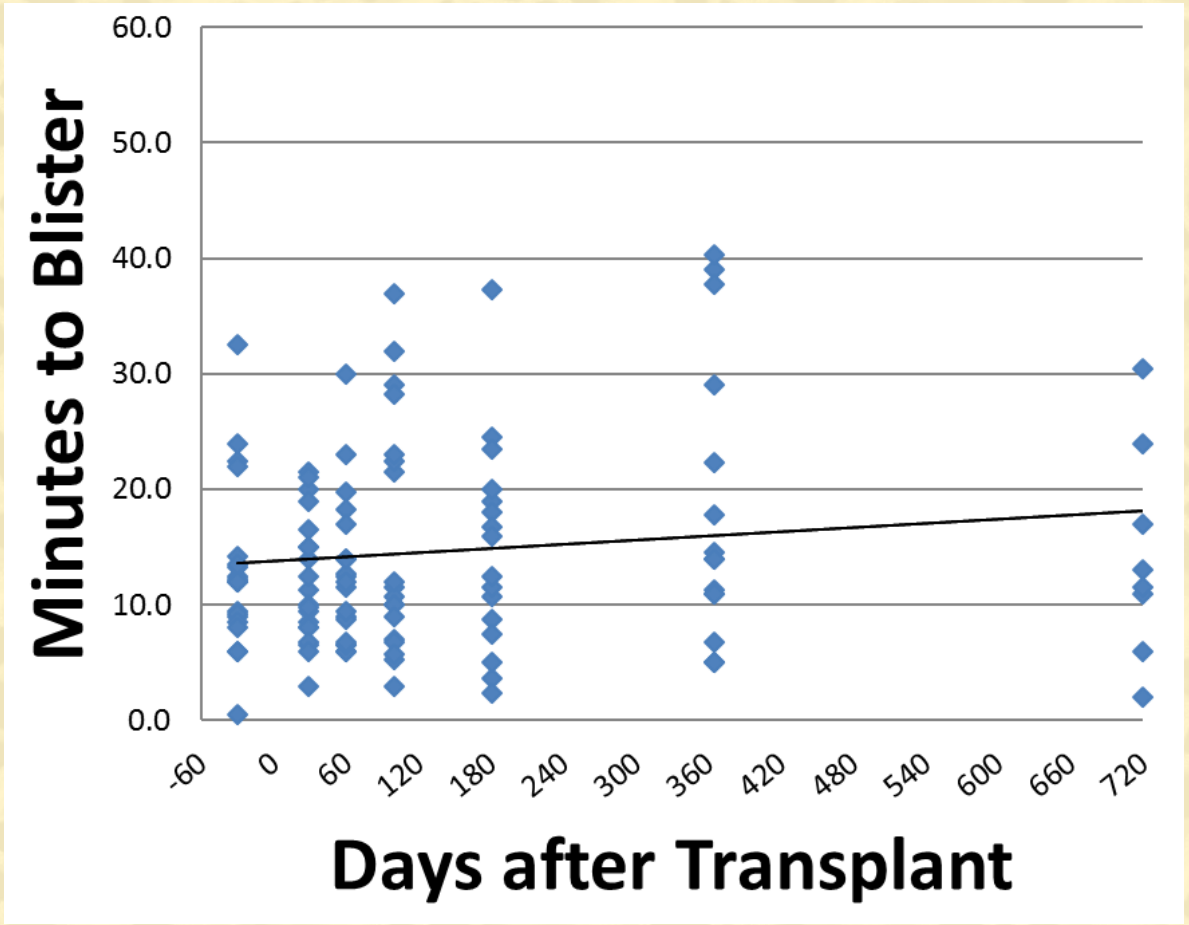


LH24



How do we know if it works?

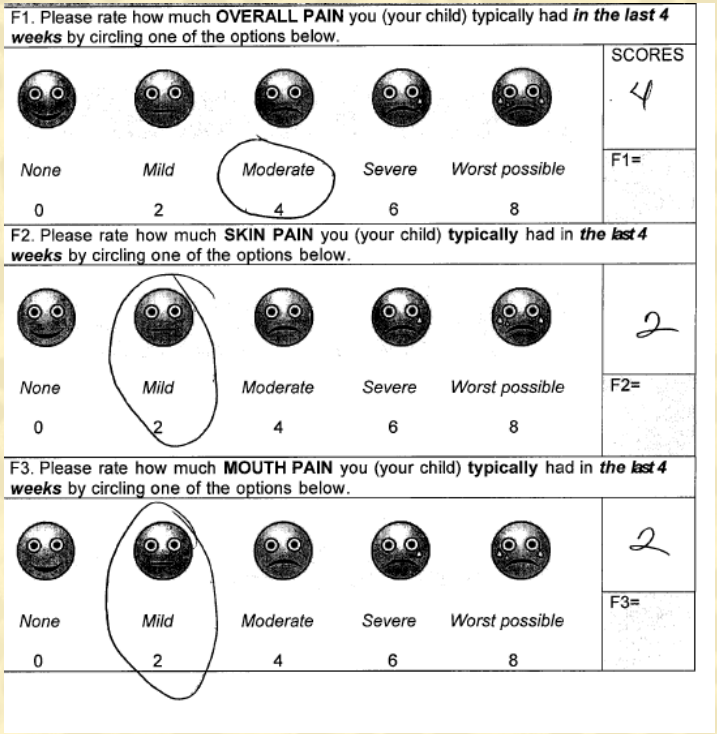
Skin strength (blistering machine)
Correlation of skin strength with skin engraftment



How do we know if it works?

Patient and parent report (iScorEB)

"Today he ate Chex, ice cream, melon, yogurt, popcorn, nachos and cheese, soft shell taco, a chocolate chip cookie, chips and salsa, and cereal with milk."



F1. Please rate how much **OVERALL PAIN** you (your child) typically had ***in the last 4 weeks*** by circling one of the options below.

SCORES 4

None 0 | Mild 2 | Moderate 4 | Severe 6 | Worst possible 8

F1=

F2. Please rate how much **SKIN PAIN** you (your child) **typically** had in ***the last 4 weeks*** by circling one of the options below.

2

None 0 | Mild 2 | Moderate 4 | Severe 6 | Worst possible 8

F2=

F3. Please rate how much **MOUTH PAIN** you (your child) **typically** had in ***the last 4 weeks*** by circling one of the options below.

2

None 0 | Mild 2 | Moderate 4 | Severe 6 | Worst possible 8

F3=

"He is standing, taking steps with support, and becoming active again."

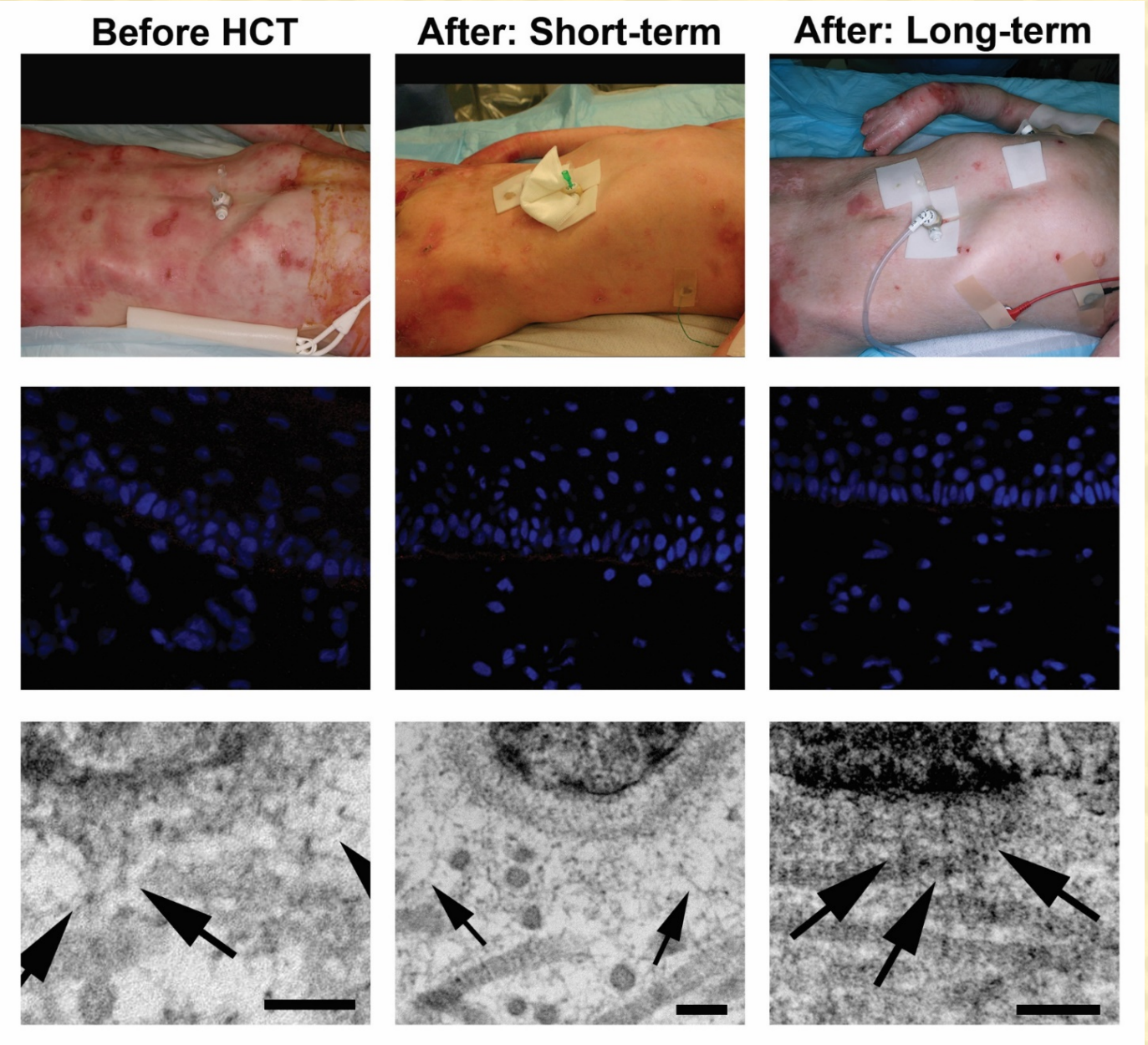
How do we know if it works?

Parent report of estimated impact on time and money

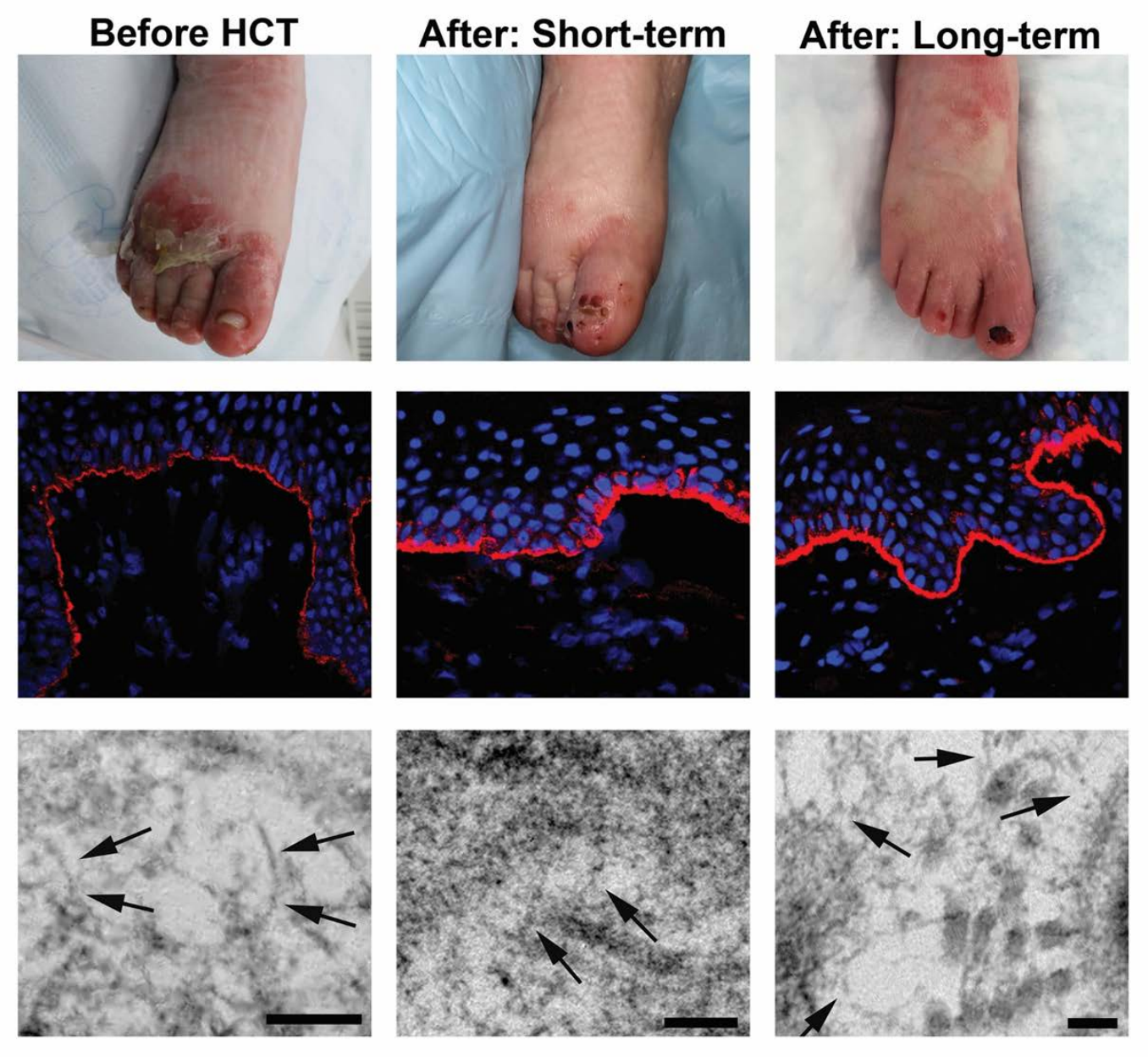
Conditioning	Transfusions	Hospital days
High dose	22.3	74.5
Low dose	6.3	38
	P=0.003	P=0.01

- **5-10 fold reduction in bandages**
- **Reduced time bandaging**
- **Fewer antibiotics and surgical interventions**

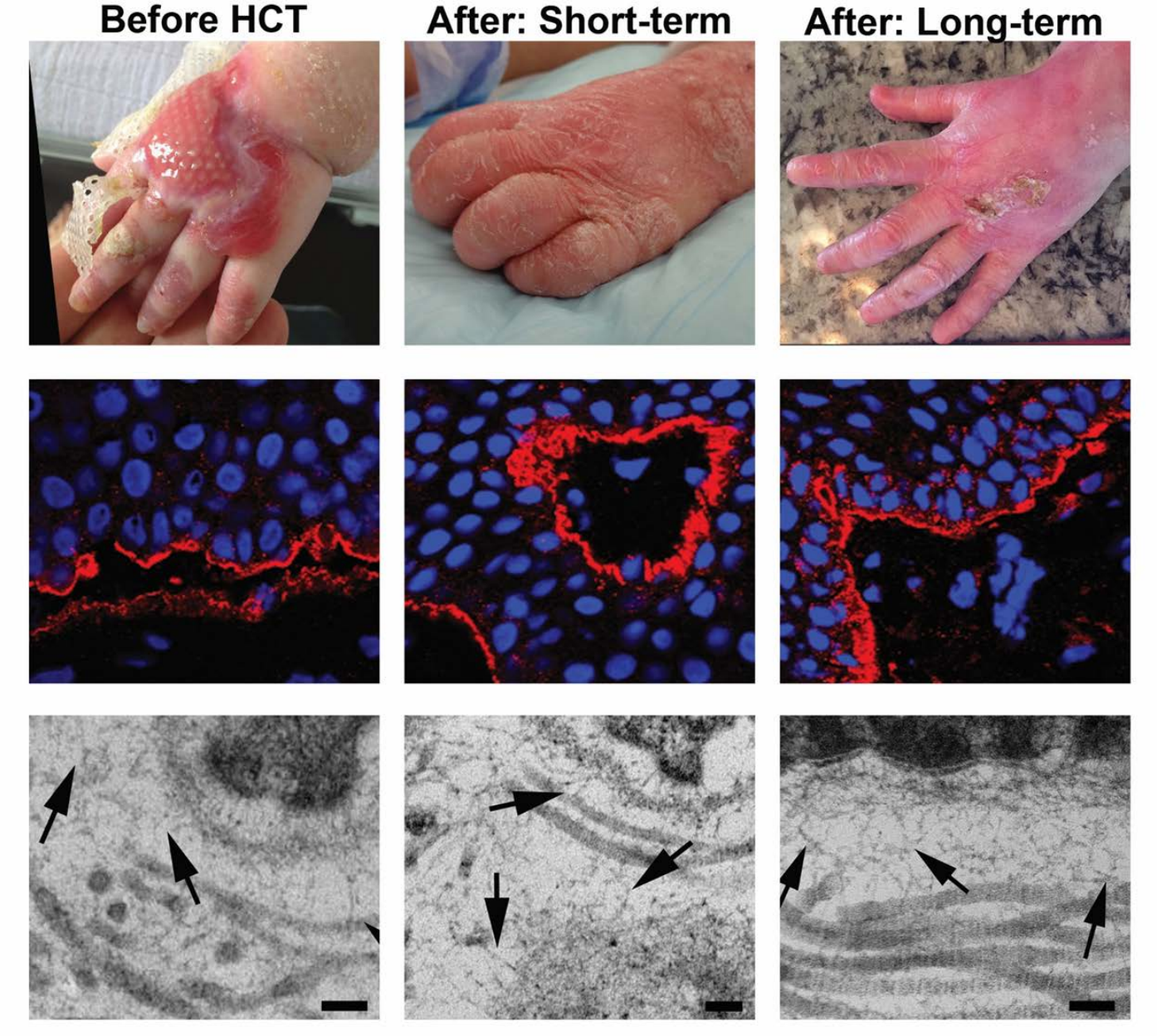
How do we know if it works?



How do we know if it works?

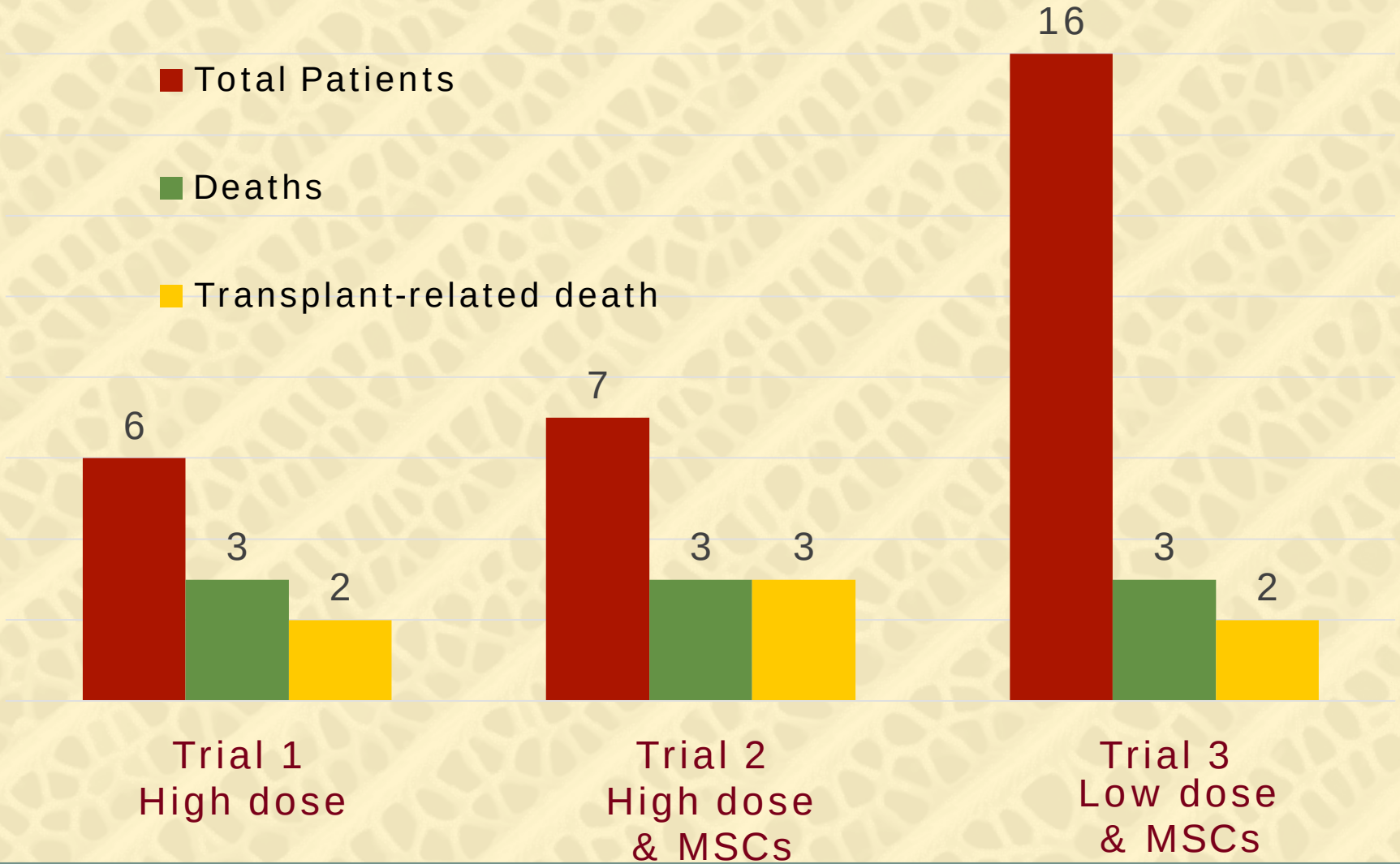


How do we know if it works?

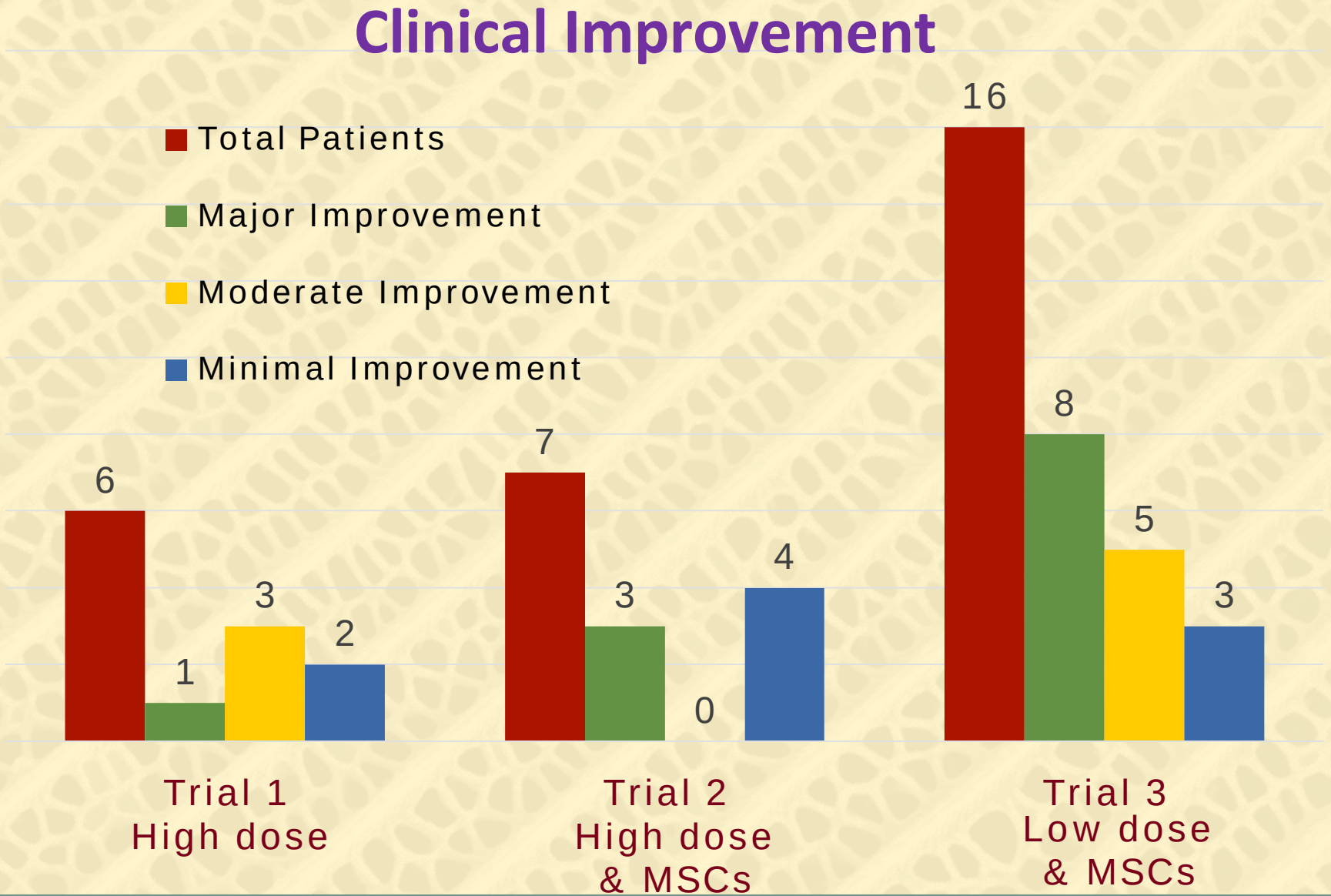


Why does the trial change?

Overall 2-year survival = 75%



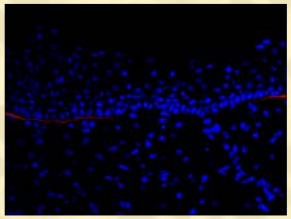
Should we do BMT for RDEB?

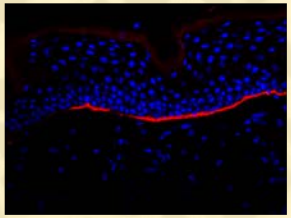


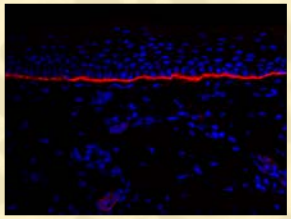
Should we do BMT for *LAMA3* JEB?

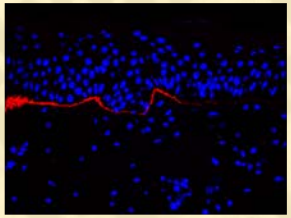
1-year-old with *LAMA3* JEB – high dose conditioning

Before transplant | **1 year after transplant**







23% donor in skin

BSA 90% before

< 5% after

Should we do BMT for *LAMA3* JEB?

10-year-old with *LAMA3* JEB – reduced intensity conditioning

Before transplant | **2 years after transplant**

50% donor in skin

BSA 75% before

< 50% after

Is HCT a cure for EB?

- **No**
- **However, thus far…only clinical intervention shown to:**
  - Correct the systemic disease pathology of RDEB
  - Have potential to improve overall quality of life

New BMT protocols for severe EB

1. Hematopoietic cells

- Haploidentical grafts

2. Mesenchymal stromal cells

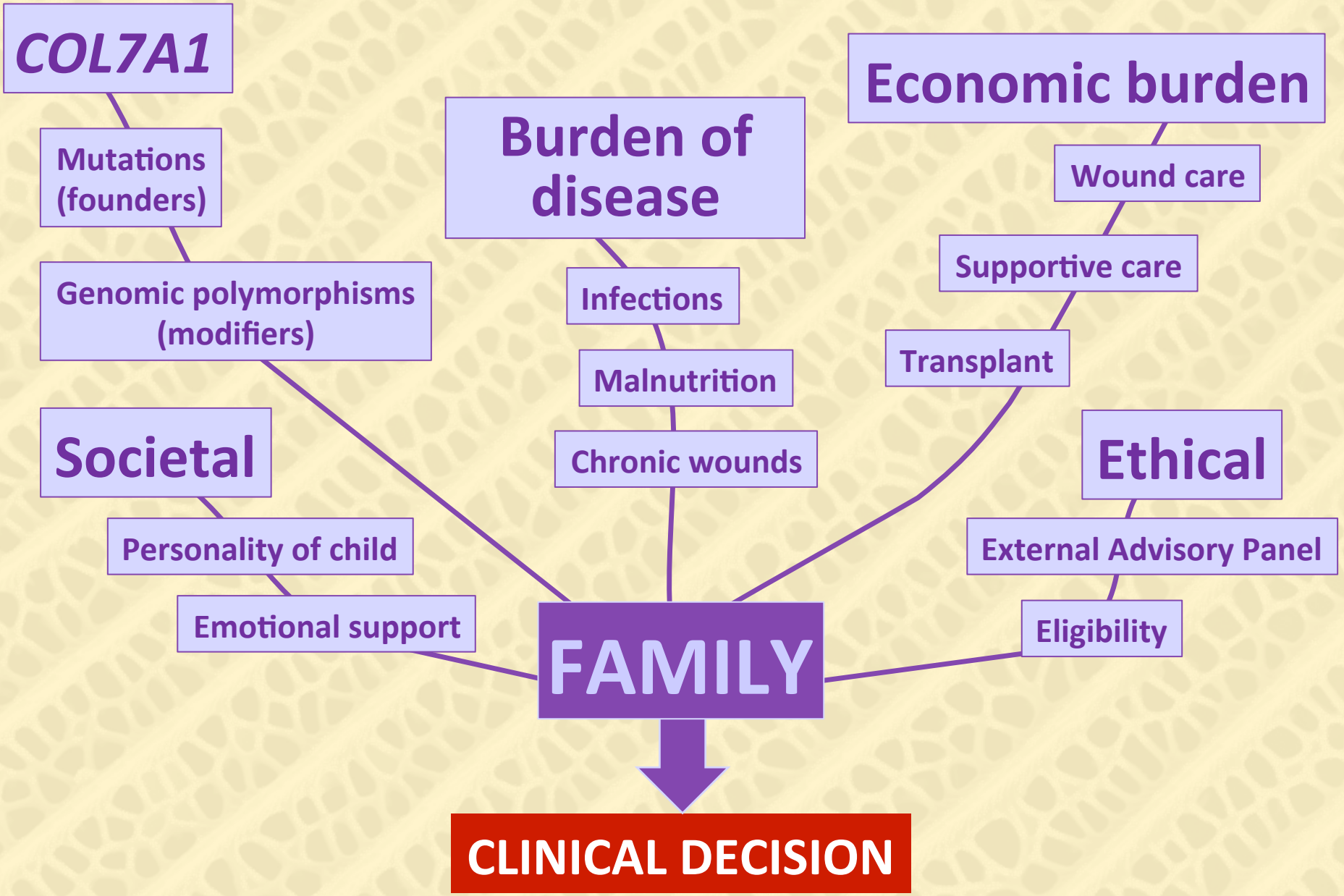
- Three serial infusions

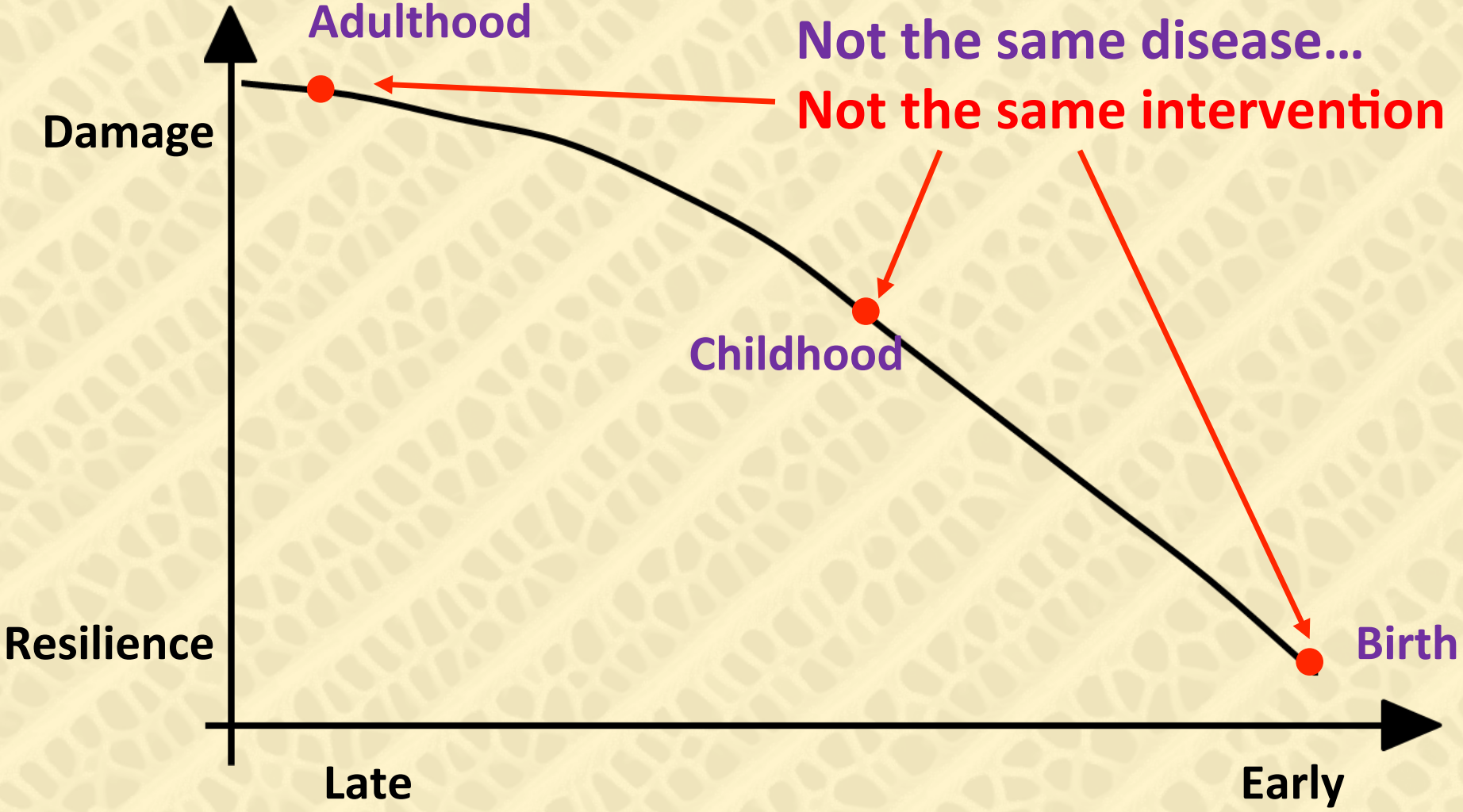
3. Epidermal cells

- Skin grafting from HCT donor
- Skin grafting from mosaic skin

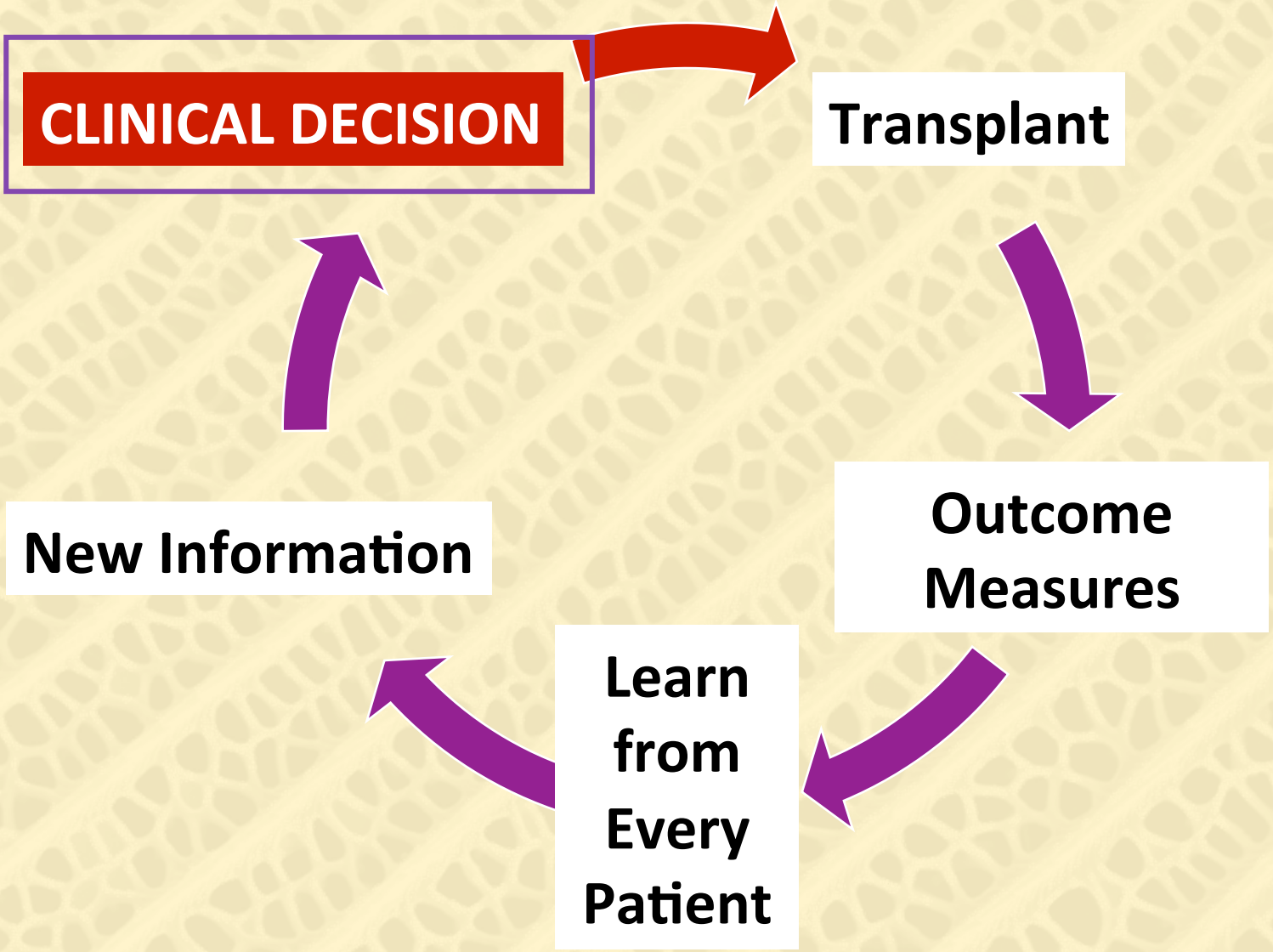

NEW HANDS NEW LIFE
BY
ZUZIA

Biomedical Moment

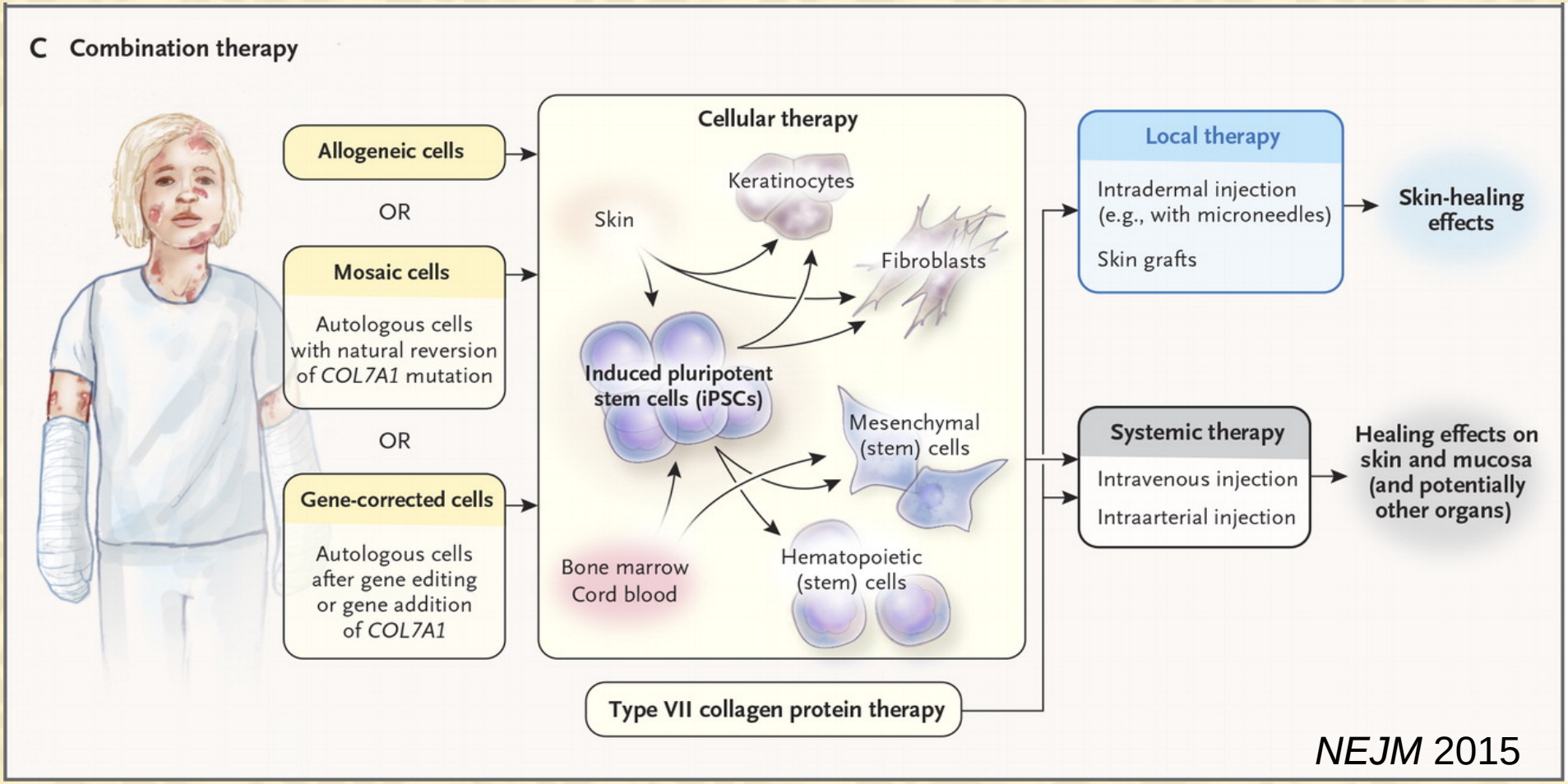



Adulthood
Not the same disease…
Not the same intervention
Damage
Childhood
Resilience
Birth
Late
Early

Cycle of learning



Combination therapy for RDEB



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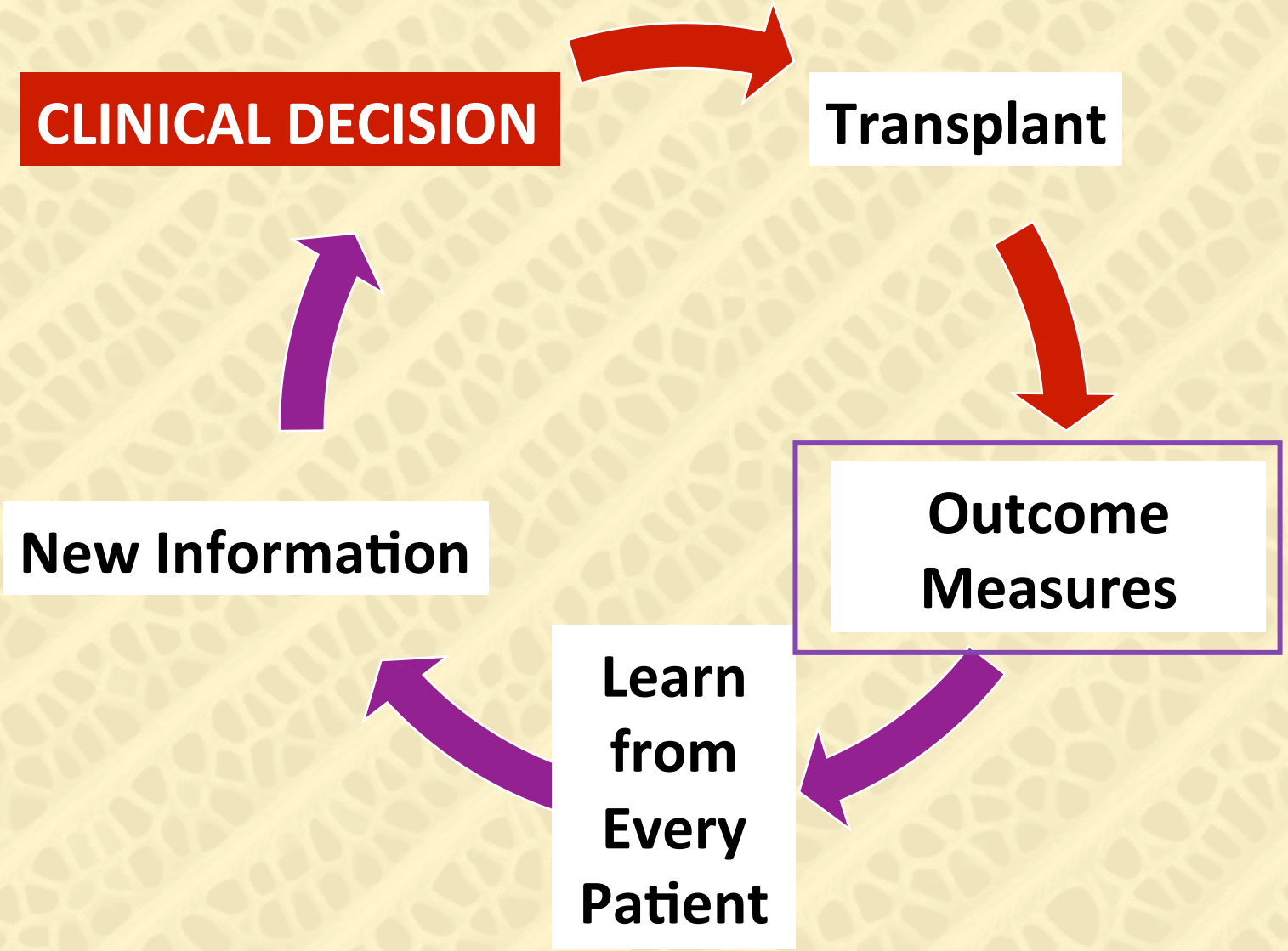
Cycle of learning

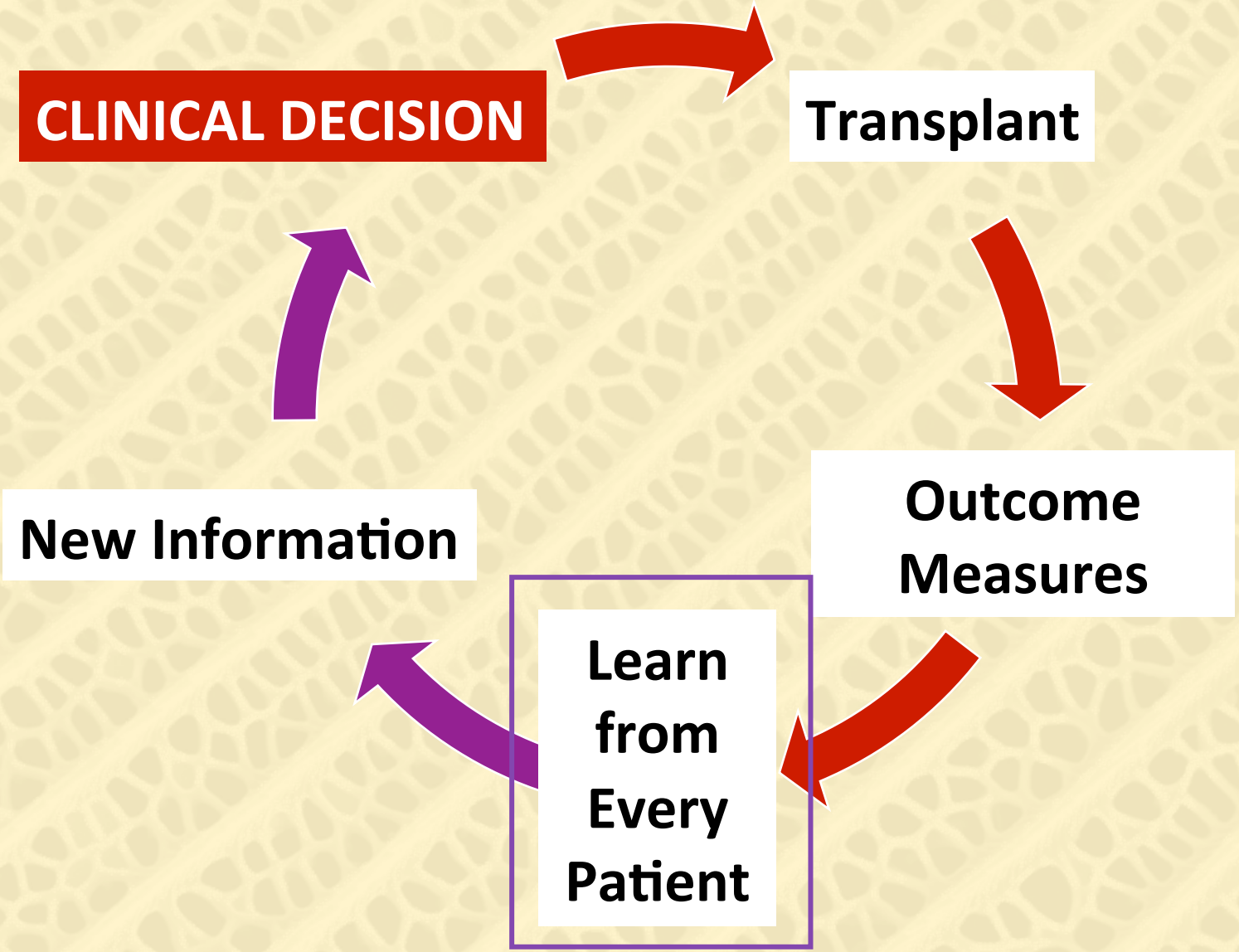


Outcome Measures

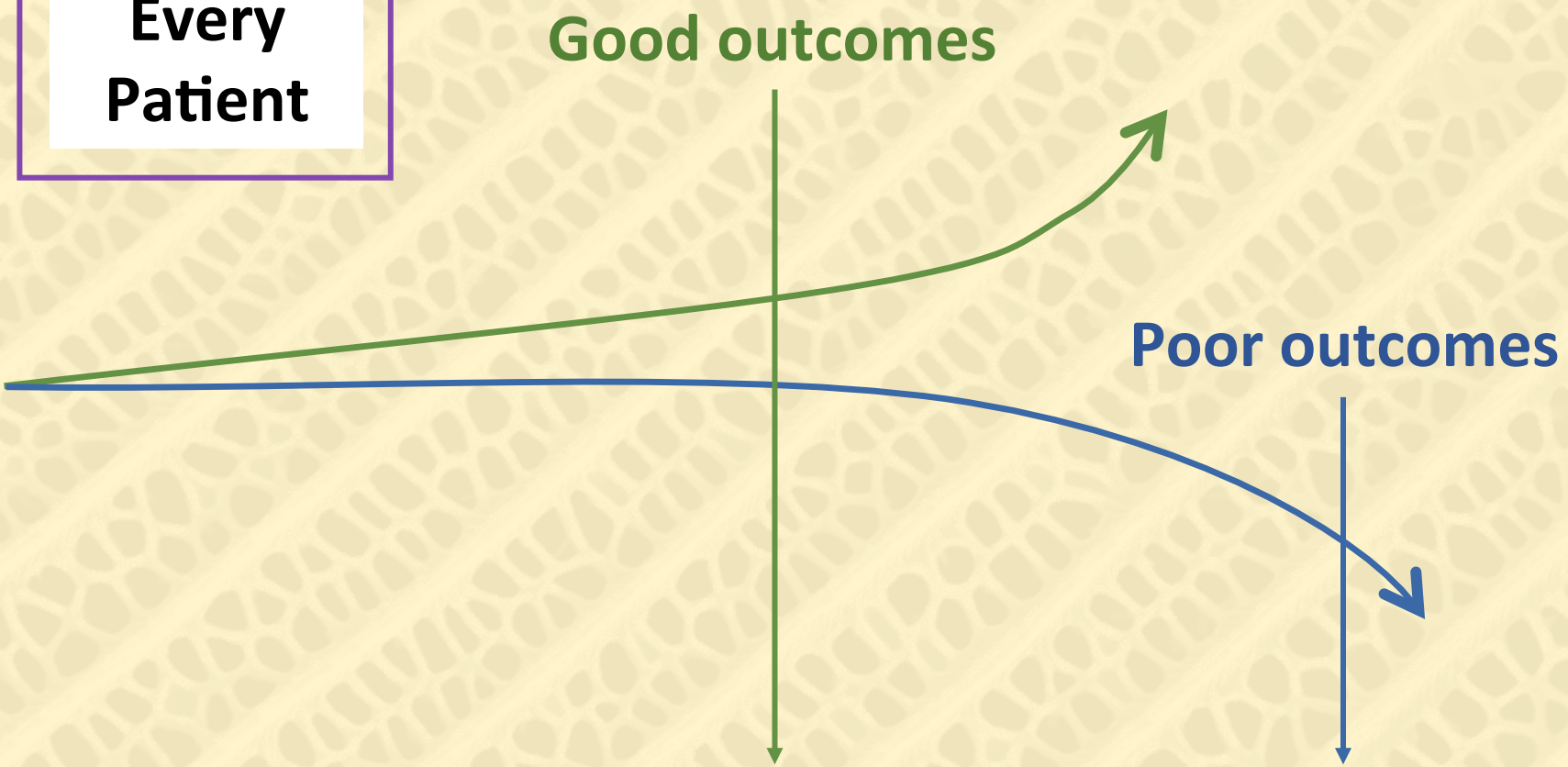
Follow-up and assessment over time

1. Biomarkers: C7, skin engraftment, anchoring fibrils
2. Skin strength
3. Wound healing, SCC
4. Time in hospital
5. Quality of life (iScorEB)

Cycle of learning

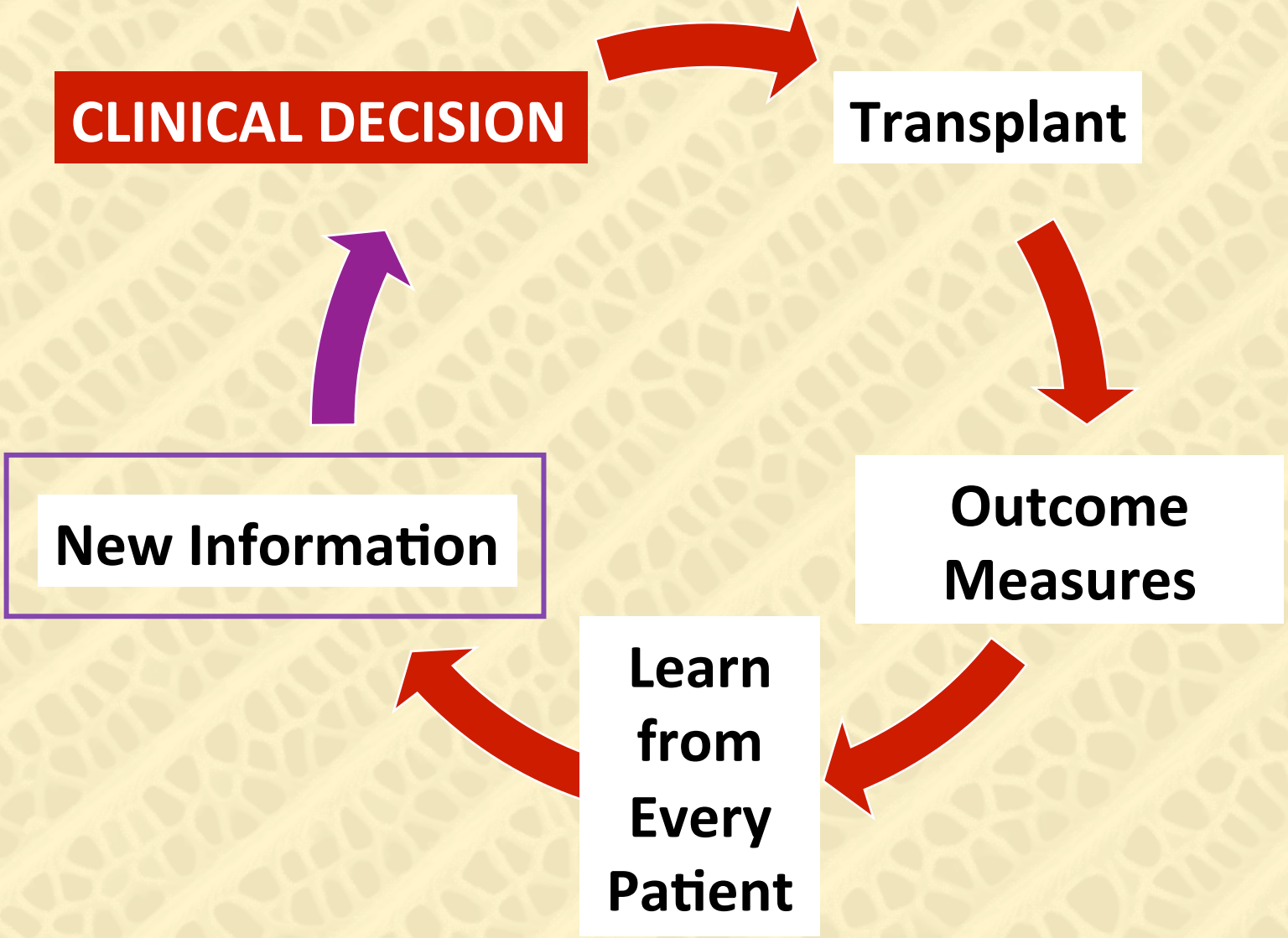


Learn from Every Patient



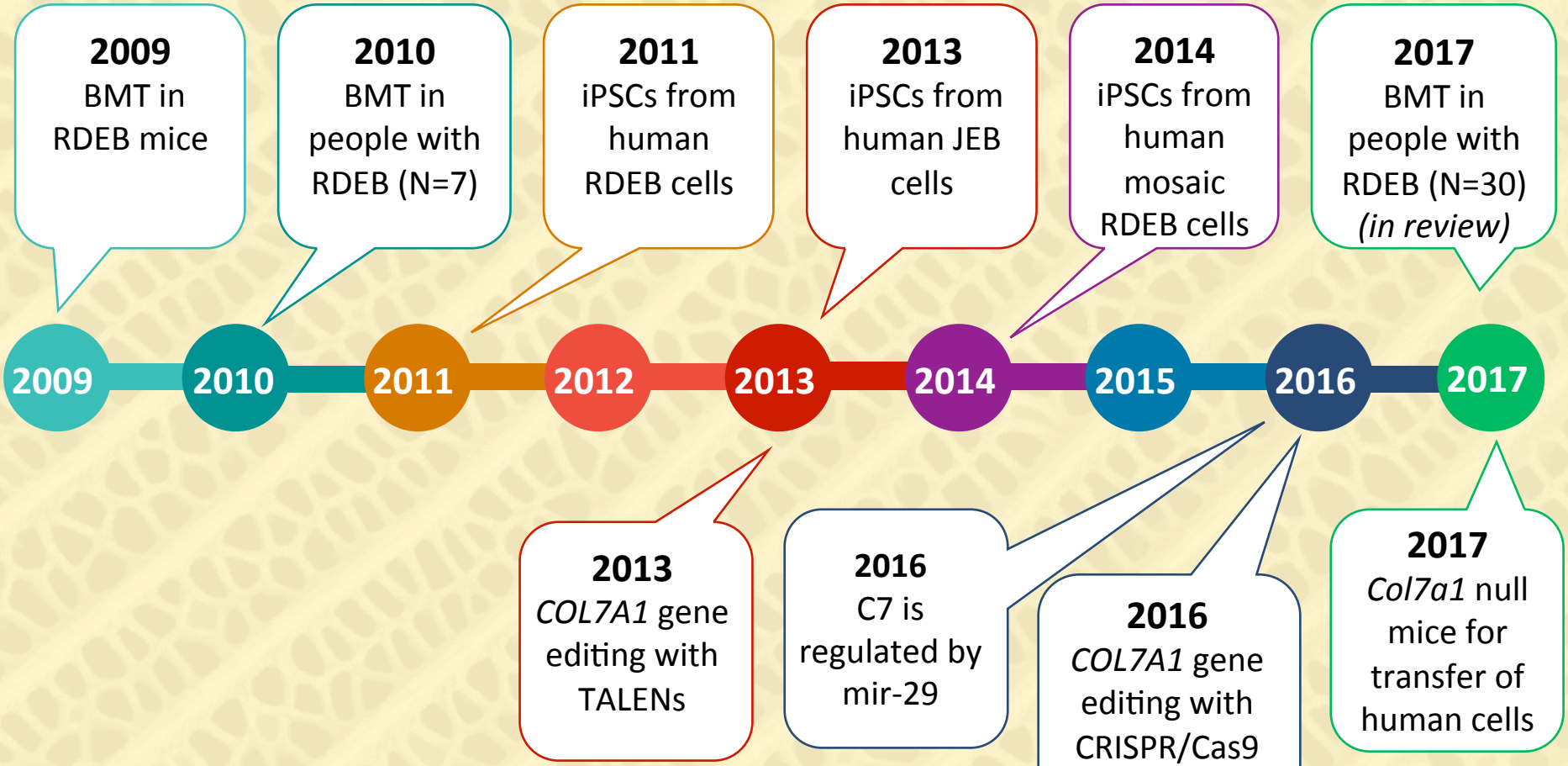
New Information

Cycle of learning

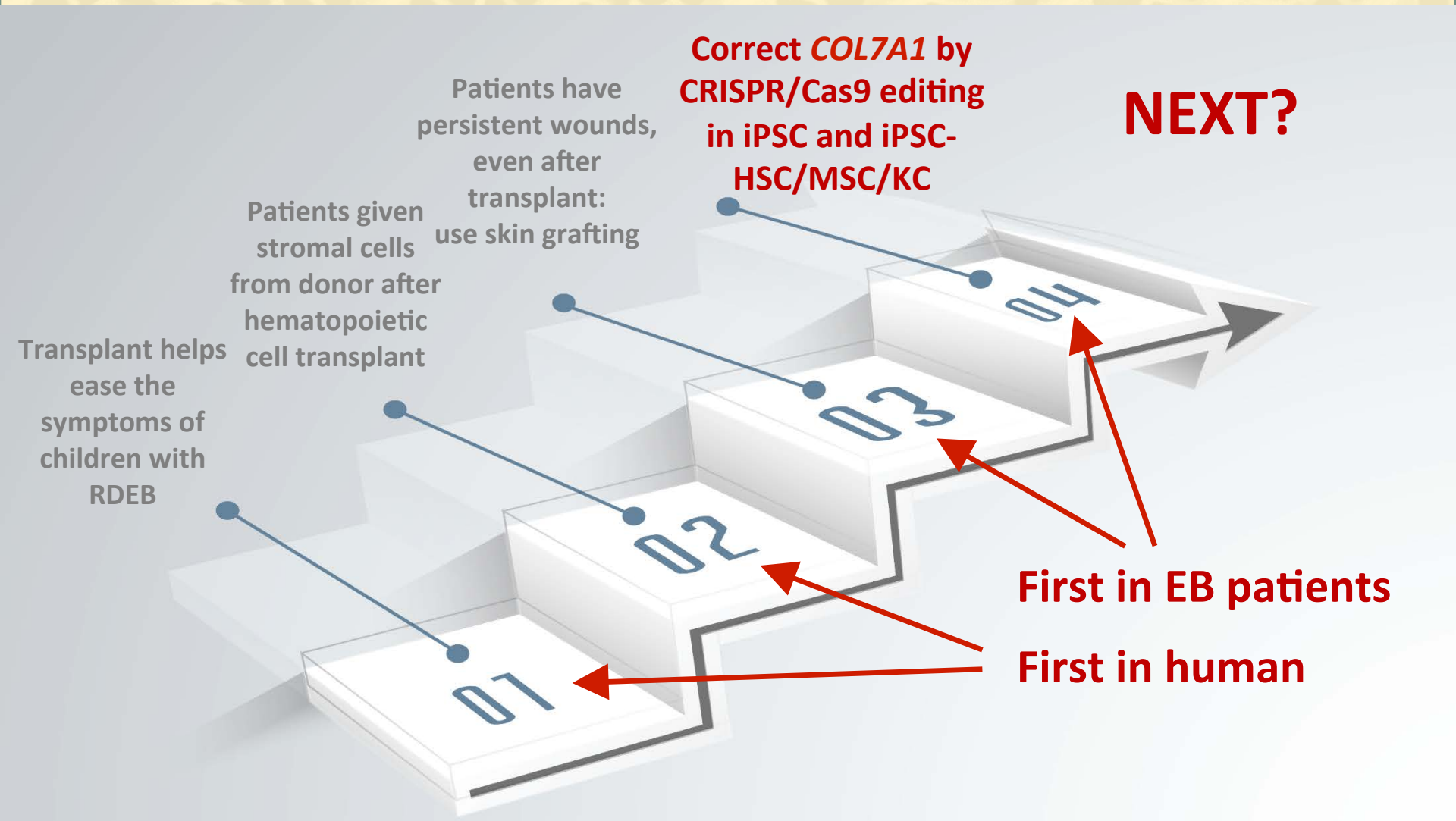


What more should we do for EB?

Cell projects

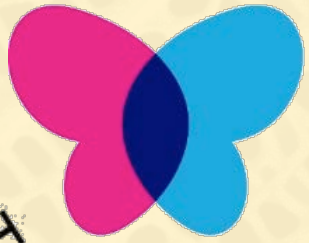


Gene projects


Correct *COL7A1* by CRISPR/Cas9 editing in iPSC and iPSC-HSC/MSC/KC
NEXT?
Patients have persistent wounds, even after transplant: use skin grafting
Patients given stromal cells from donor after hematopoietic cell transplant
Transplant helps ease the symptoms of children with RDEB
04
03
02
01
First in EB patients
First in human

Collaborators and friends

John A. McGrath
Katsuto Tamai
Alain Hovnanian
Mark Osborn
Kristen Hook
Leena Bruckner-Tuderman
Jemma Mellerio
Anne Lucky
Elena Pope
Amy Paller
Michelle de Luca
Francis Palisson
Gabi Pohla-Gubo
Denis Roop
Peter Marinkovich
Jouni Uitto



EB RESEARCH PARTNERSHIP

debra International.

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second skin second chance

EB MRF

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