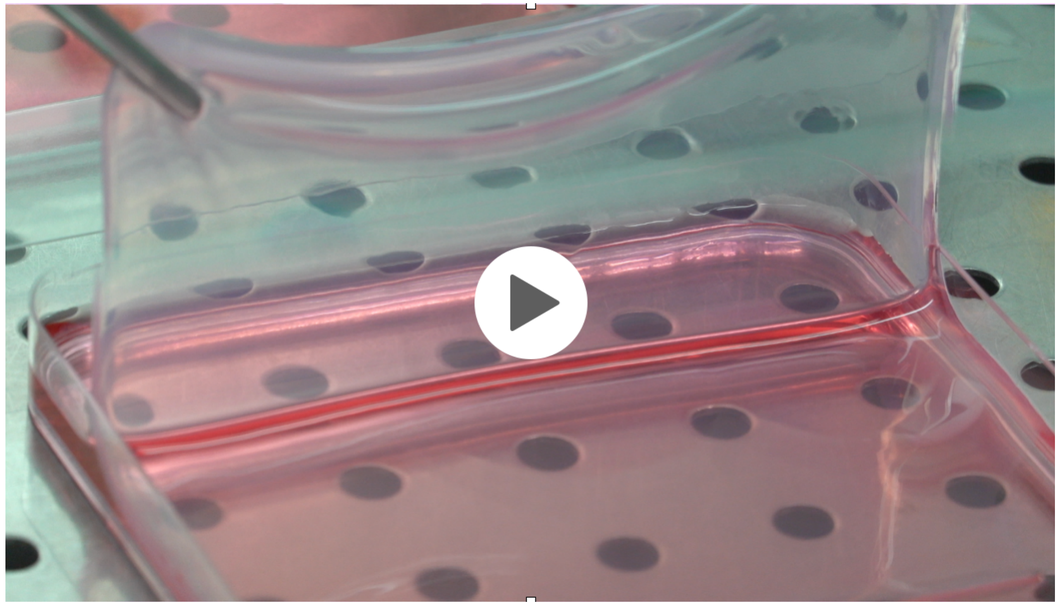
EPITHELIAL STEM CELLS IN CELL AND GENE THERAPY

PLASTIC

FIBRIN



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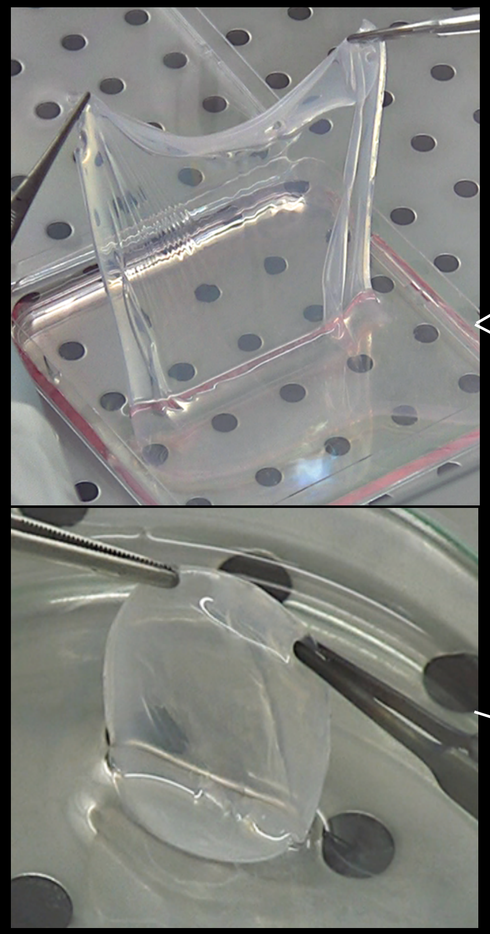
EPITHELIAL STEM CELLS IN REGENERATIVE MEDICINE

fibrin-cultured
human epidermis



fibrin-cultured
corneal epithelium

SKIN BURNS

LIFE-SAVING - THOUSANDS OF PATIENTS TREATED
UP TO 30 YEARS FOLLOW-UP - UP TO 95% OF THE BODY

GENE THERAPY
(EPIDERMOLYSIS BULLOSA)

OCULAR BURNS

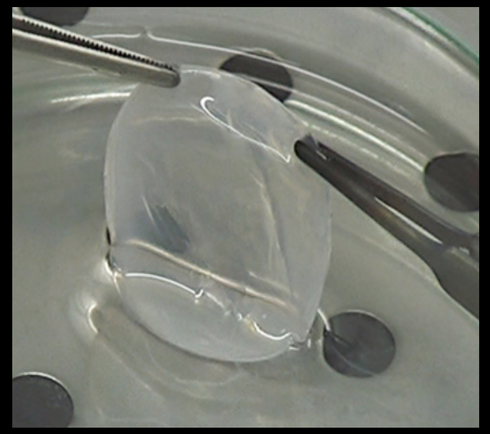
O'Connor et al. *Lancet* 1981
Gallico et al. *N.Engl.J.Med.* 1984
Pellegrini et al., *Lancet* 1997
Rama et al., *N.Engl.J.Med.* 2010
Mavilio et al., *Nat.Med.* 2006
Hirsch et al., *Nature* 2017

EPITHELIAL STEM CELLS IN REGENERATIVE MEDICINE

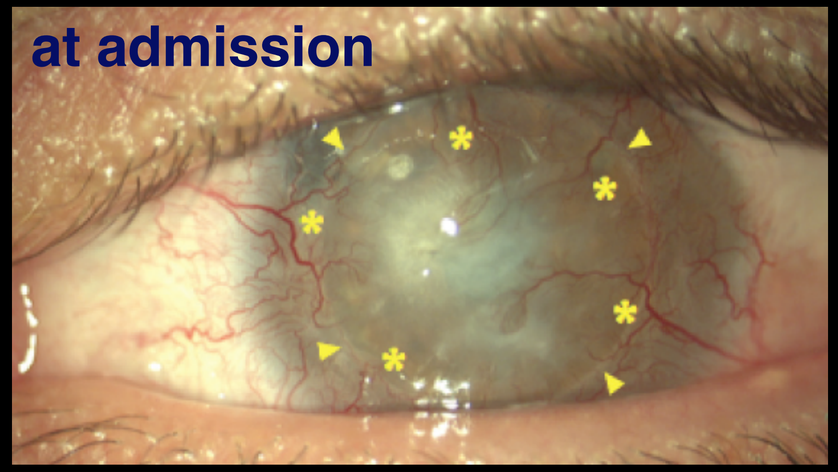
OCULAR BURNS

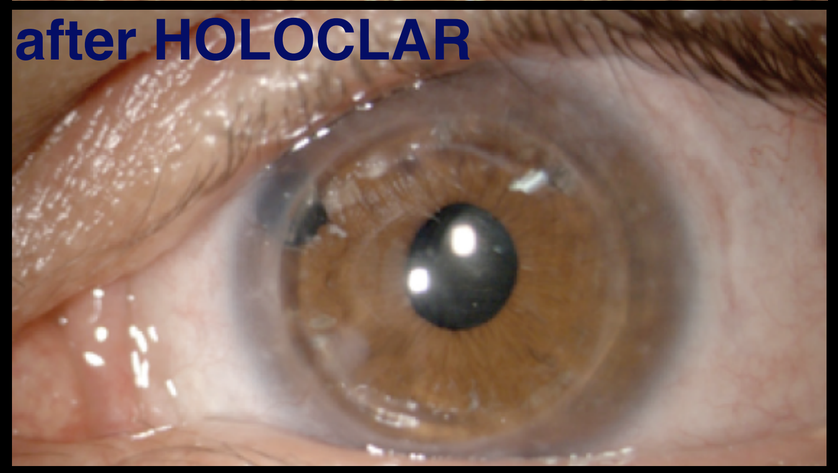
February 2015:
EMA, Registration: HOLOCLAR®

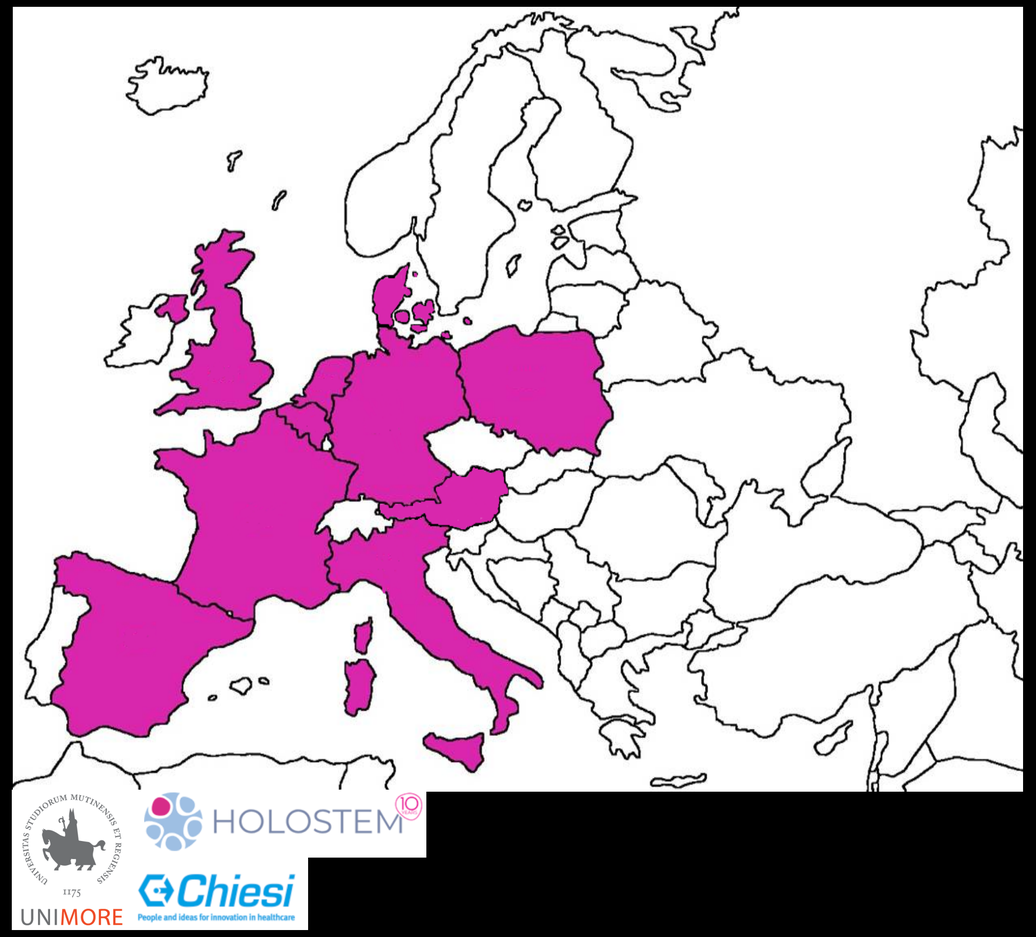
HOLOCLAR



fibrin-cultured
corneal epithelium

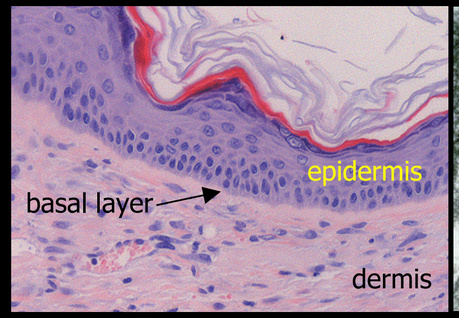




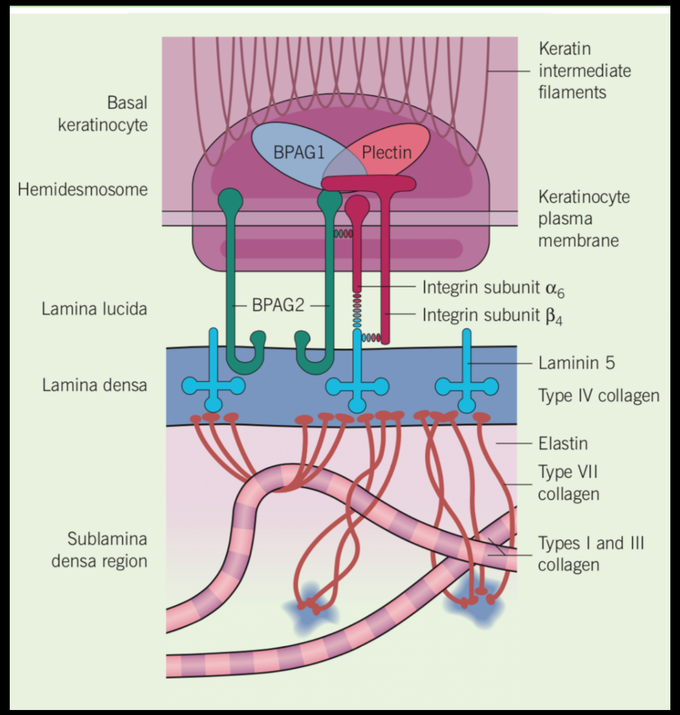


Pellegrini et al., *The Lancet*, 1997
Rama et al., *Transplantation*, 2001
Pellegrini et al., *N.Engl.J.Med.*, 2004
Rama et al., *N.Engl.J.Med.*, 2010
Pellegrini et al., *Regen.Med.* 2013
Pellegrini et al., *Regen. Med.* 2016

Inherited EPIDERMOLYSIS BULLOSA (EB): “the butterfly children”



Epidermal-dermal junction



EB

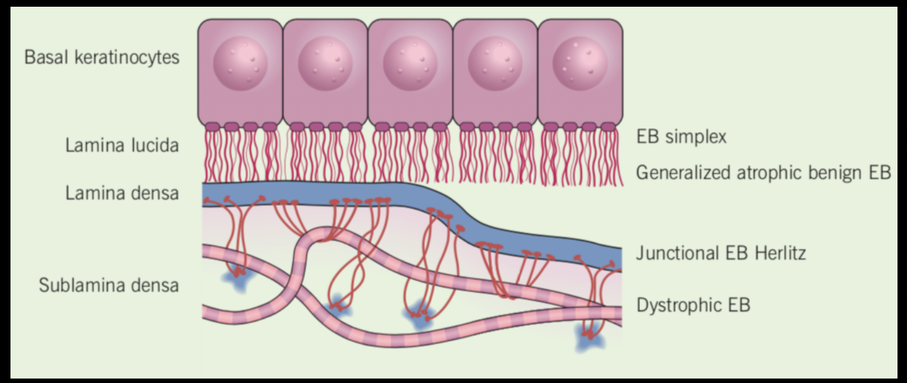
SIMPLEX:
keratins 5/14

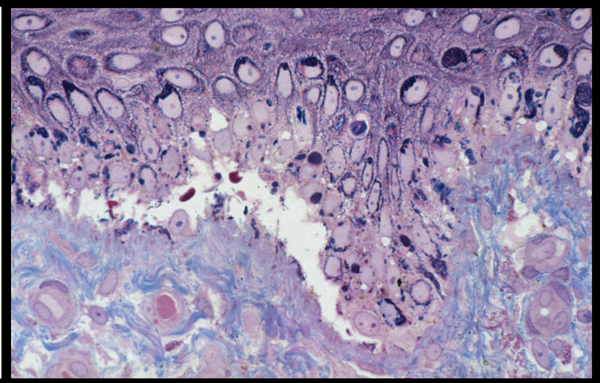
JUNCTIONAL:
laminin 5, α6β4, collagen XVII

DYSTROPHIC:
Collagen VII

Devastating skin *BLISTERING*, Very *POOR QUALITY OF LIFE*

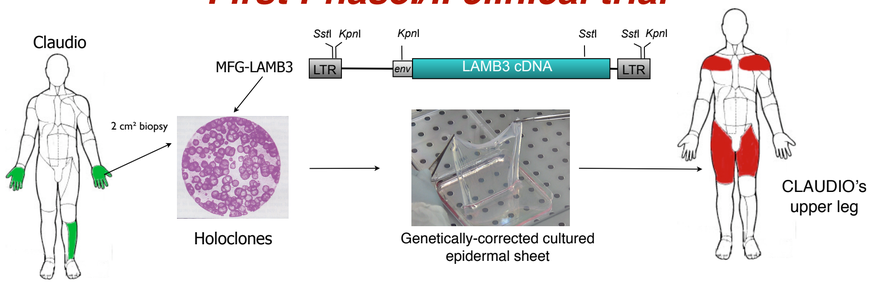
SHORT LIFE EXPECTANCY
Squamous Cell Carcinoma

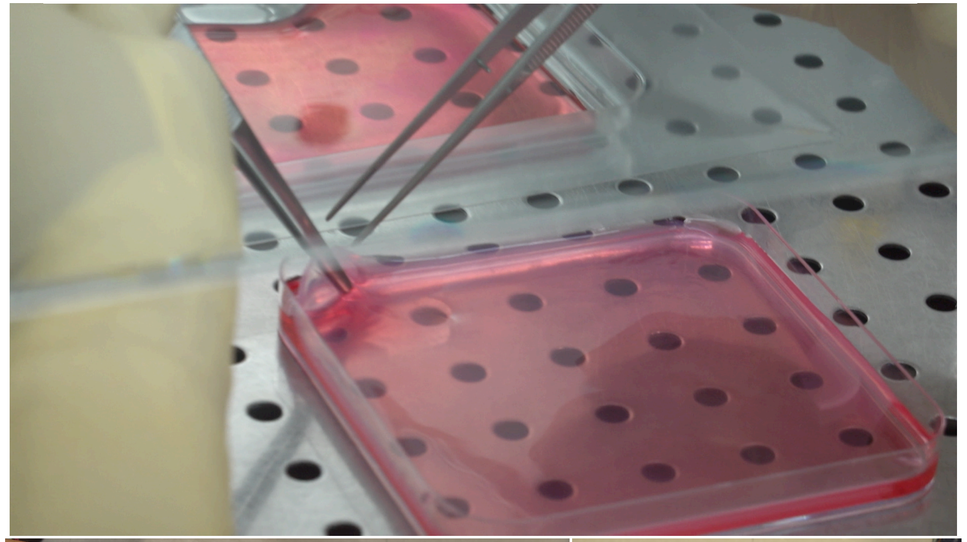




Combined cell and gene therapy for Junctional Epidermolysis Bullosa

First Phase I/II clinical trial





transgenic autologous epidermal cultures

nature medicine

2006

Correction of junctional epidermolysis bullosa by transplantation of genetically modified epidermal stem cells

Fulvio Mavilio[1], Graziella Pellegrini[1,2], Stefano Ferrari[2], Francesca Di Nunzio[1], Enzo Di Iorio[2], Alessandra Recchia[1], Giulietta Maruggi[1], Giuliana Ferrari[3], Elena Provasi[4], Chiara Bonini[4], Sergio Capurro[5], Andrea Conti[6], Cristina Magnoni[6], Alberto Giannetti[6] & Michele De Luca[1,2]

Stem Cell Reports

2014

ISSCR

Report

OPEN ACCESS

Long-Term Stability and Safety of Transgenic Cultured Epidermal Stem Cells in Gene Therapy of Junctional Epidermolysis Bullosa

Laura De Rosa,[1,5] Sonia Carulli,[1,5] Fabienne Cocchiarella,[1] Daniela Quaglino,[2] Elena Enzo,[1] Eleonora Franchini,[1] Alberto Giannetti,[3] Giorgio De Santis,[4] Alessandra Recchia,[1] Graziella Pellegrini,[1] and Michele De Luca[1,*]

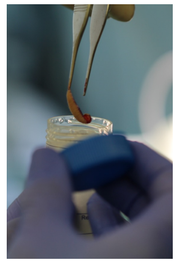
2017

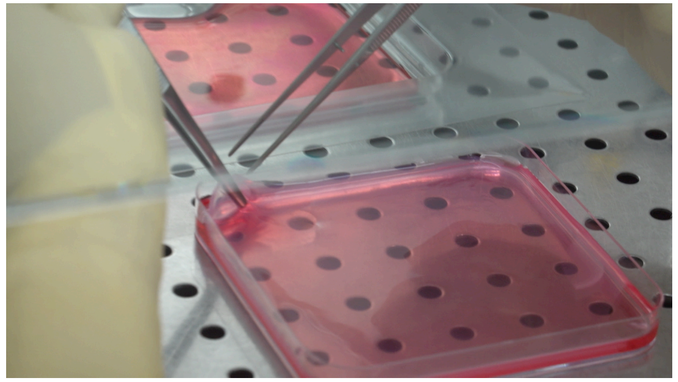
J Invest Dermatol. 2017 Mar;137(3):778-781. doi: 10.1016/j.jid.2016.10.038. Epub 2016 Nov 10.

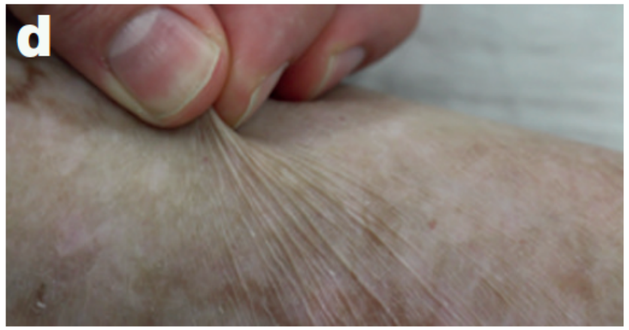
Closure of a Large Chronic Wound through Transplantation of Gene-Corrected Epidermal Stem Cells.

Bauer JW[1], Koller J[2], Murauer EM[3], De Rosa L[4], Enzo E[4], Carulli S[5], Bondanza S[5], Recchia A[4], Muss W[6], Diem A[7], Mayr E[3], Schlager P[3], Gratz IK[8], Pellegrini G[4], De Luca M[4].

COMBINED CELL AND GENE THERAPY FOR JUNCTIONAL EPIDERMOLYSIS BULLOSA



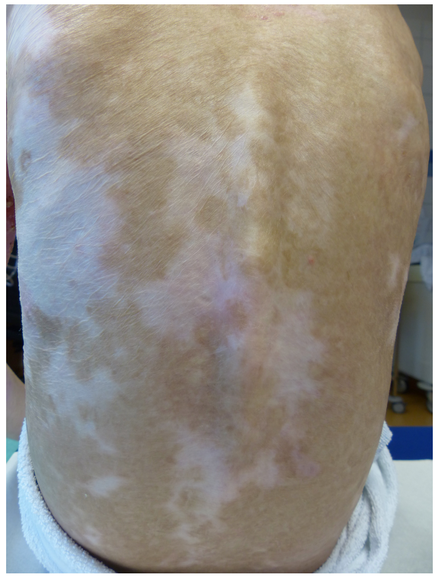


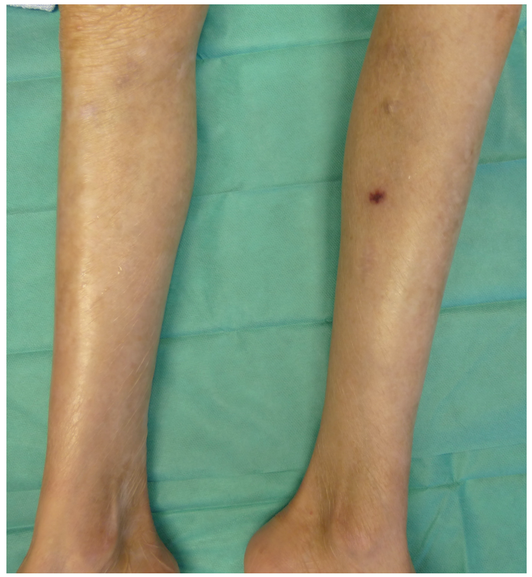


Hirsch et al, *Nature*, 2017

OCTOBER 2020, *5 YEARS*

Kueckelhaus et al, *Submitted*





No blisters in transplanted areas

Normal wound healing upon injury

No adverse events

No pain, no itch

Normal mechanoception, nociception

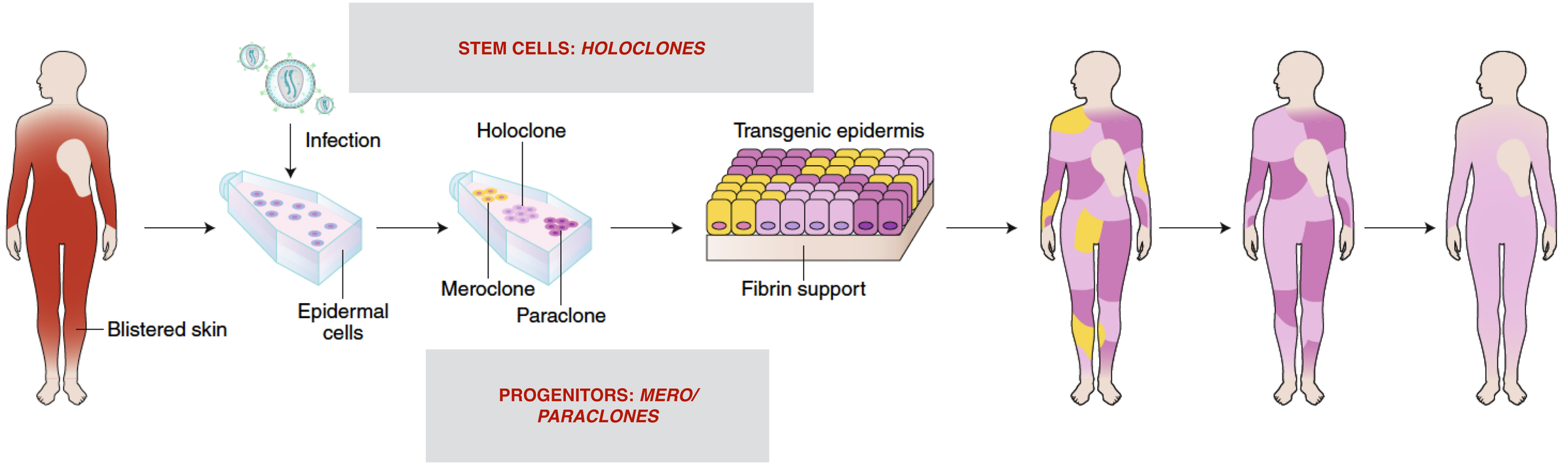
No need for ointment or creams

Dyschromia and decreased elastin fibers

The human epidermis is sustained only by *long-lived self-renewing stem cells (holoclones)* generating pools of transient progenitors (meroclones and paraclones)

Hirsch et al., *Nature*, 2017
De Luca et al., *Nature Cell Biol*, 2019
De Rosa et al., *CSH series*, 2019

Clonal tracing using proviral integrations as clonal genetic marks



CLINICAL TRIALS for HOLOGENE 5 and HOLOGENE 7

Junctional EB

HOLOGENE 5
Combined ex vivo cell and gene therapy by means of *LAMB3*-RV-transduced epidermal stem cells

→ **EMA: protocol advice**

↓

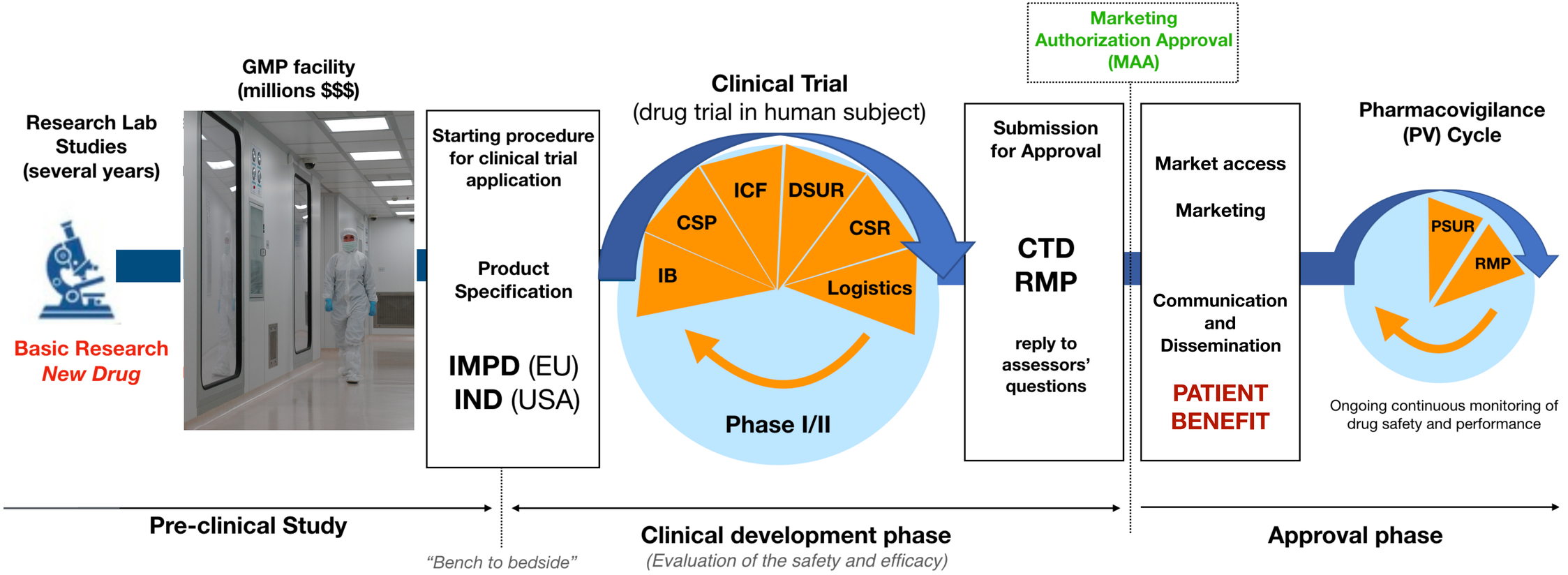
Phase II/III Trial ongoing

Recessive Dystrophic EB

HOLOGENE 7
Combined ex vivo cell and gene therapy by means of *COL7A1*-RV-transduced epidermal stem cells

→ **Phase I/II Trial**

Directive EU/1394/2007 on Advanced Therapy Medicinal Products (as cell and gene therapy)



IMPD-Investigational Medical Product Dossier (EU)
IND-Investigational New Drug (USA)

IB-Investigator's Brochure
CSP-Clinical Study Protocol
ICF-Informed Consent Forms
DSUR-Development Safety Update Report
CSR-Clinical Study Report

CTD-Common Technical Document
PSUR-Safety Update Report
RMP-Risk Management Plan Update