Burn Wound Treatment-From the Clinic to the Lab and Back

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Service of Plastic, Reconstructive & Hand Surgery [CPR]
University Hospital of Lausanne, Switzerland

Why cell therapy and skin substitutes? The example of burn patients

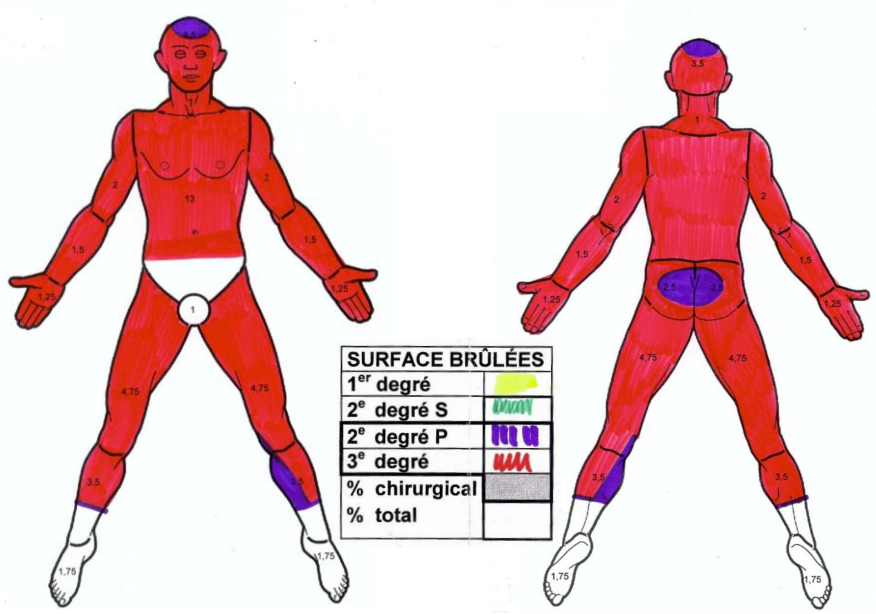
Burns

- 1500 hosp./yr. In CH
- CHUV burn center 400,000 cm^2/yr

Skin grafts remain the first choice to treat major burn patients

- Split thickness skin grafts
- Full thickness skin grafts

Healthy skin insufficient on major burn patients



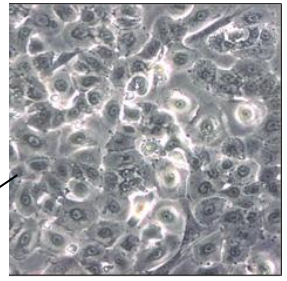
Cultured autologous epithelial sheets (CEA)

Rheinwald and Green [1975]

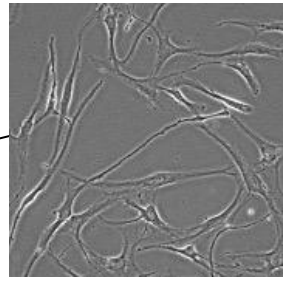
Clinical use [1981]

CHUV [1985]

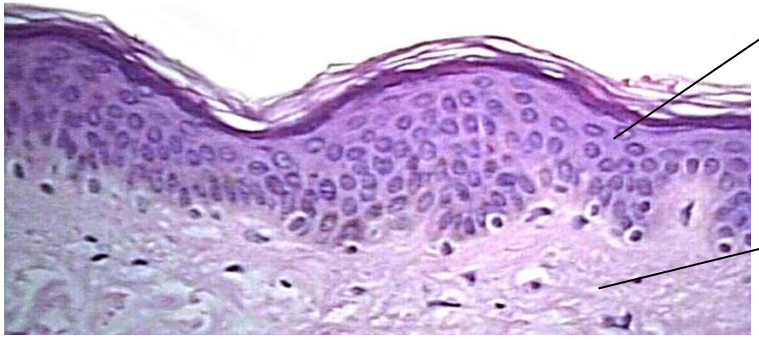
Keratinocytes

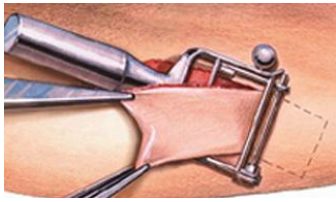


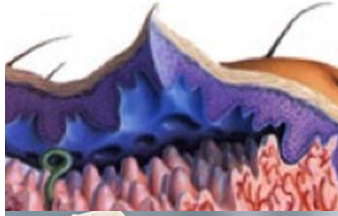
Fibroblasts



Specific cells after culture





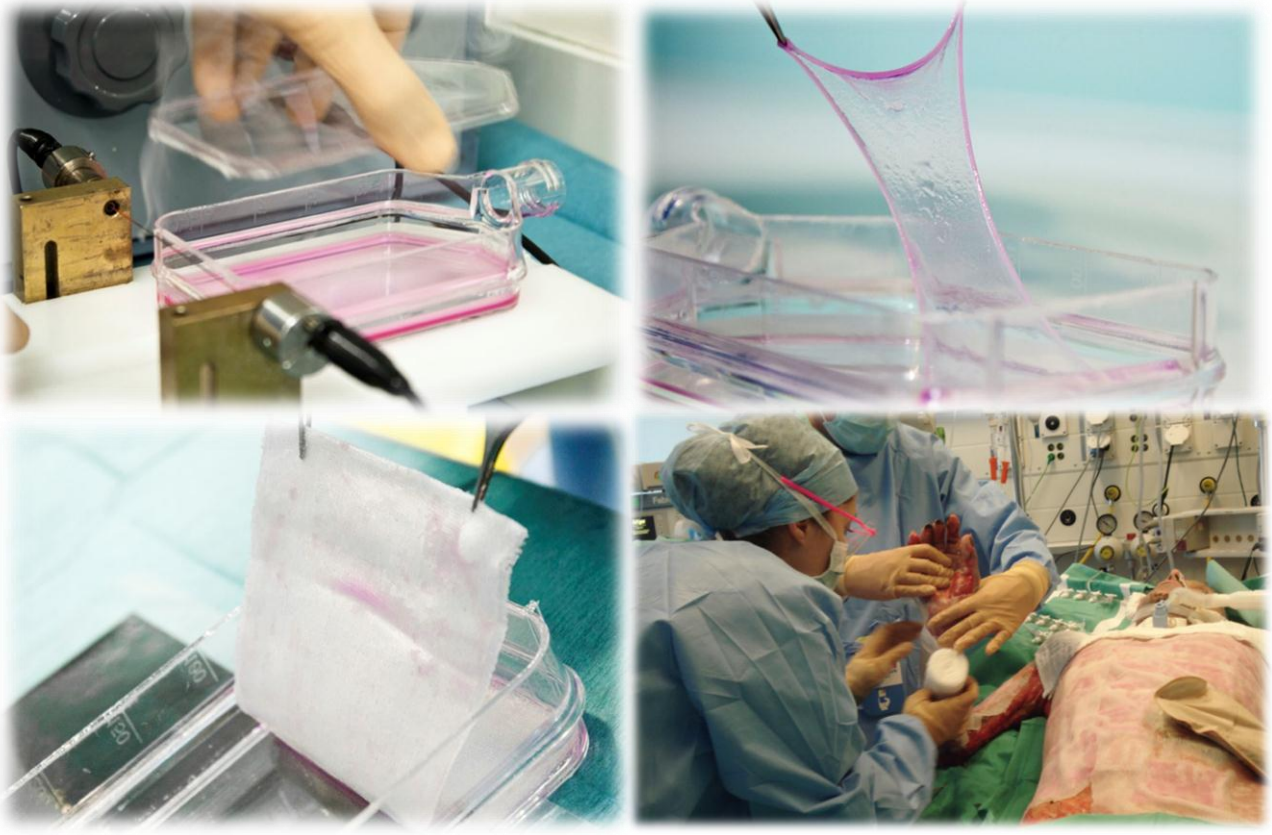


Routine integration of Cell Therapy >30 years in CHUV

- Use for TBSA from 12-95%
  - 2nd degree deep and 3rd degree burns
- Lower mortality
- Lower donor-site surface necessary
  - Fewer secondary wounds

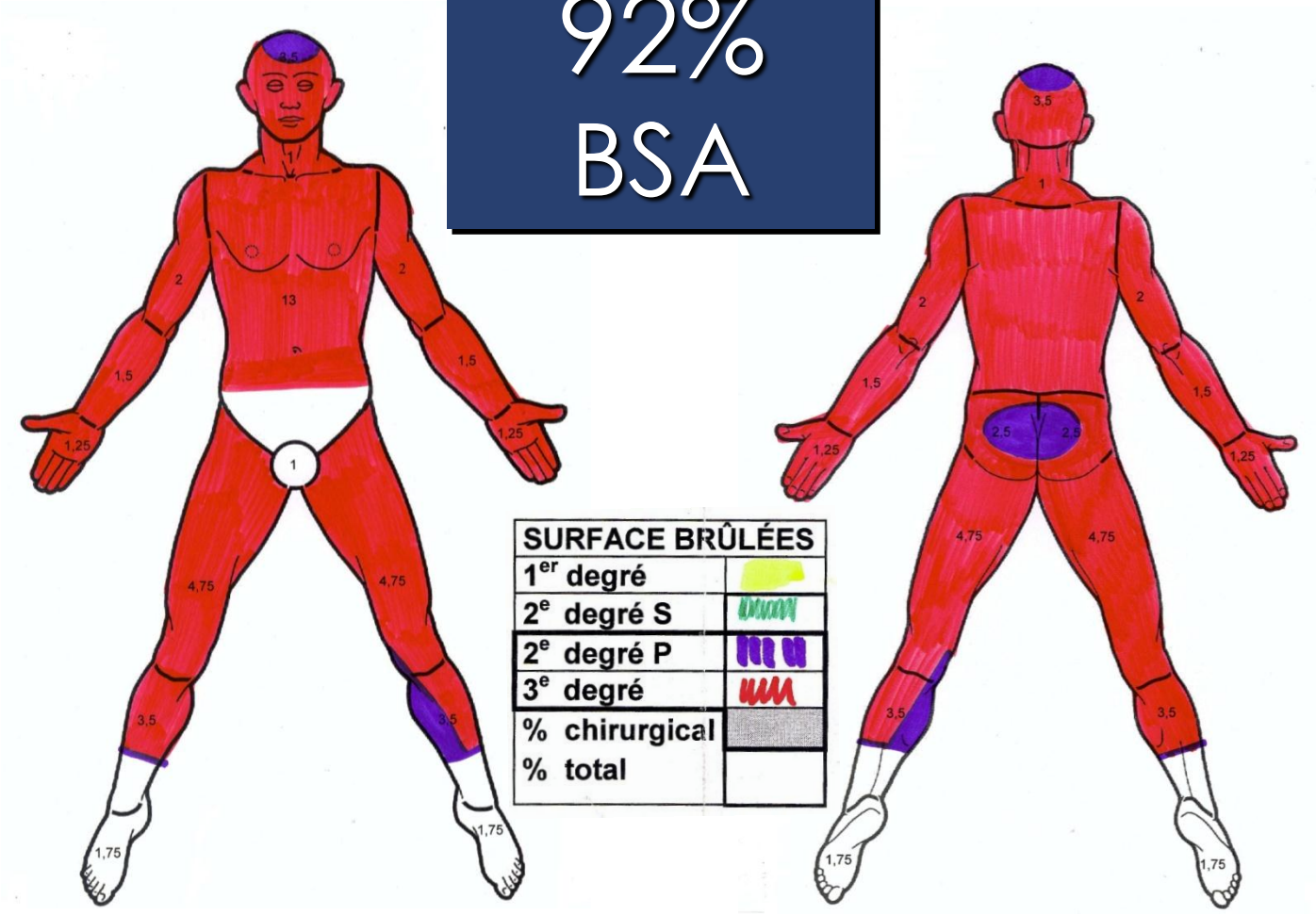
Cultured autologous epithelial sheets…

- The sheet is attached to vaseline-coated gauze and grafted

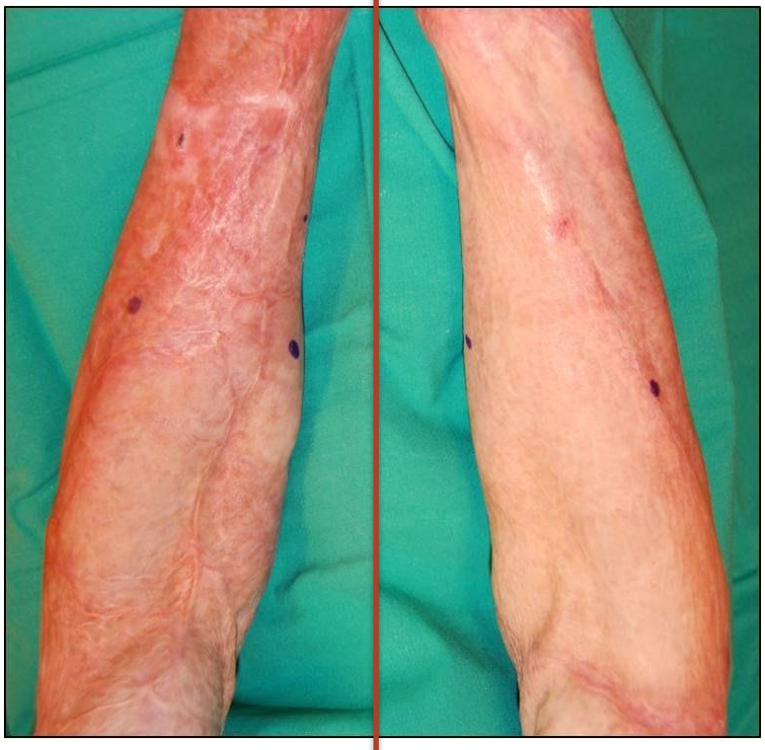


Lack of available healthy skin…

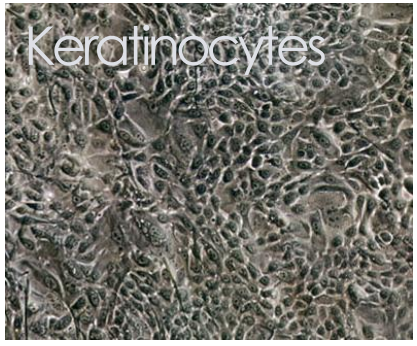
92%
BSA



Cell culture assisted surgery



Keratinocytes



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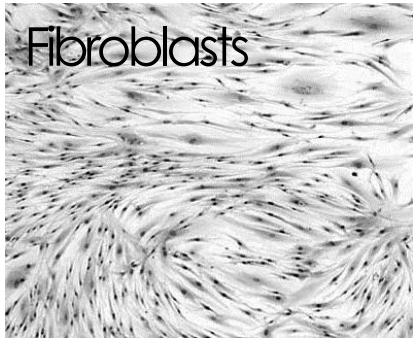


Keratinocytes

+

Fibroblasts

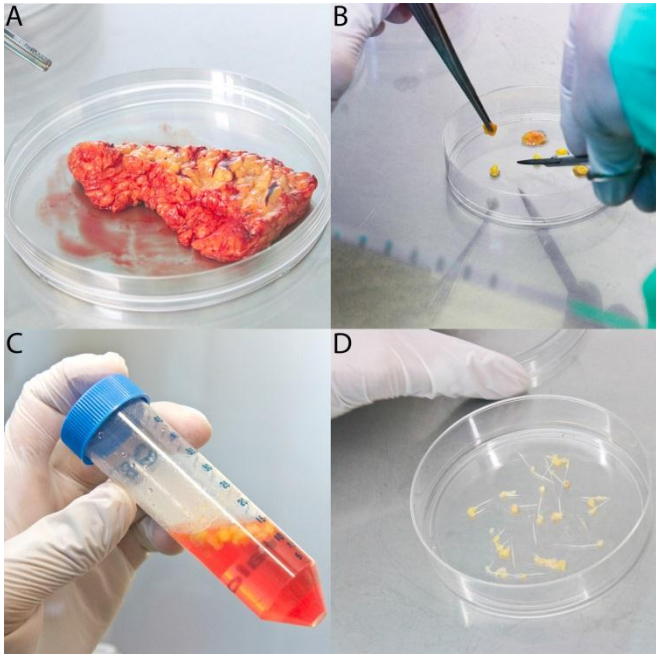
Cell culture assisted surgery

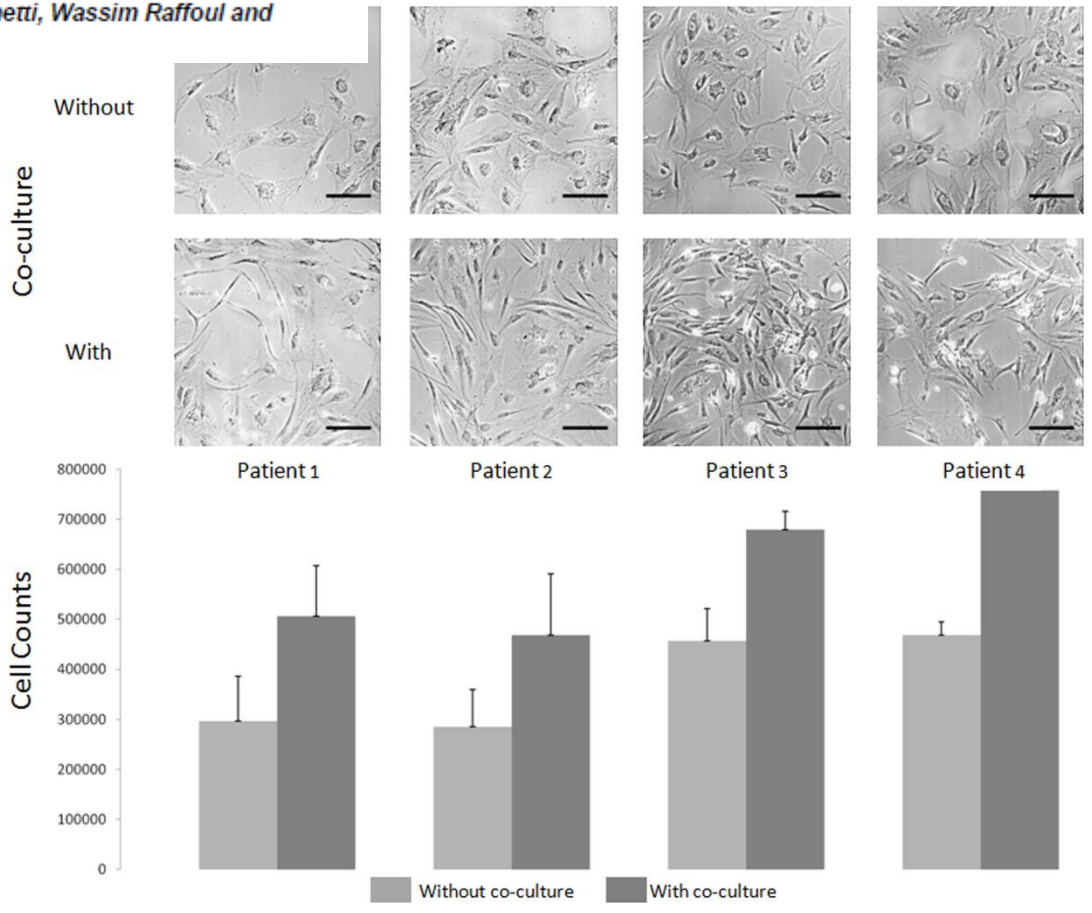
International Journal of
Stem Cell Research & Therapy
Research Article: Open Access

Krähenbühl, 2015

Enhancement of Human Adipose-Derived Stem Cell Expansion and Stability for Clinical use

*Swenn Maxence Krähenbühl, Anthony Grognuz, Murielle Michetti, Wassim Raffoul and Lee Ann Applegate**

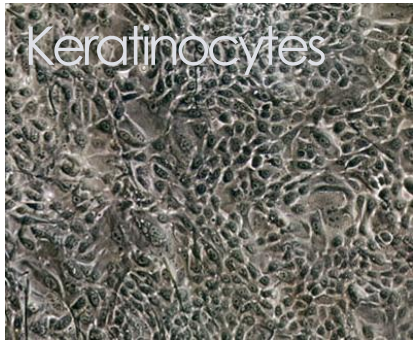




Cell therapy assisted surgery

Keratinocytes
3 weeks

Keratinocytes
+
Fibroblasts
5-6 weeks



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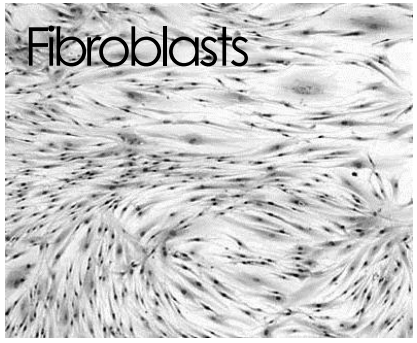
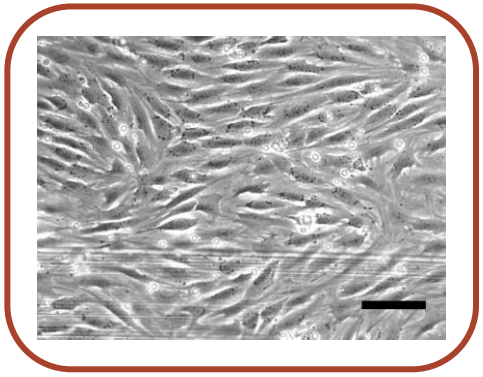
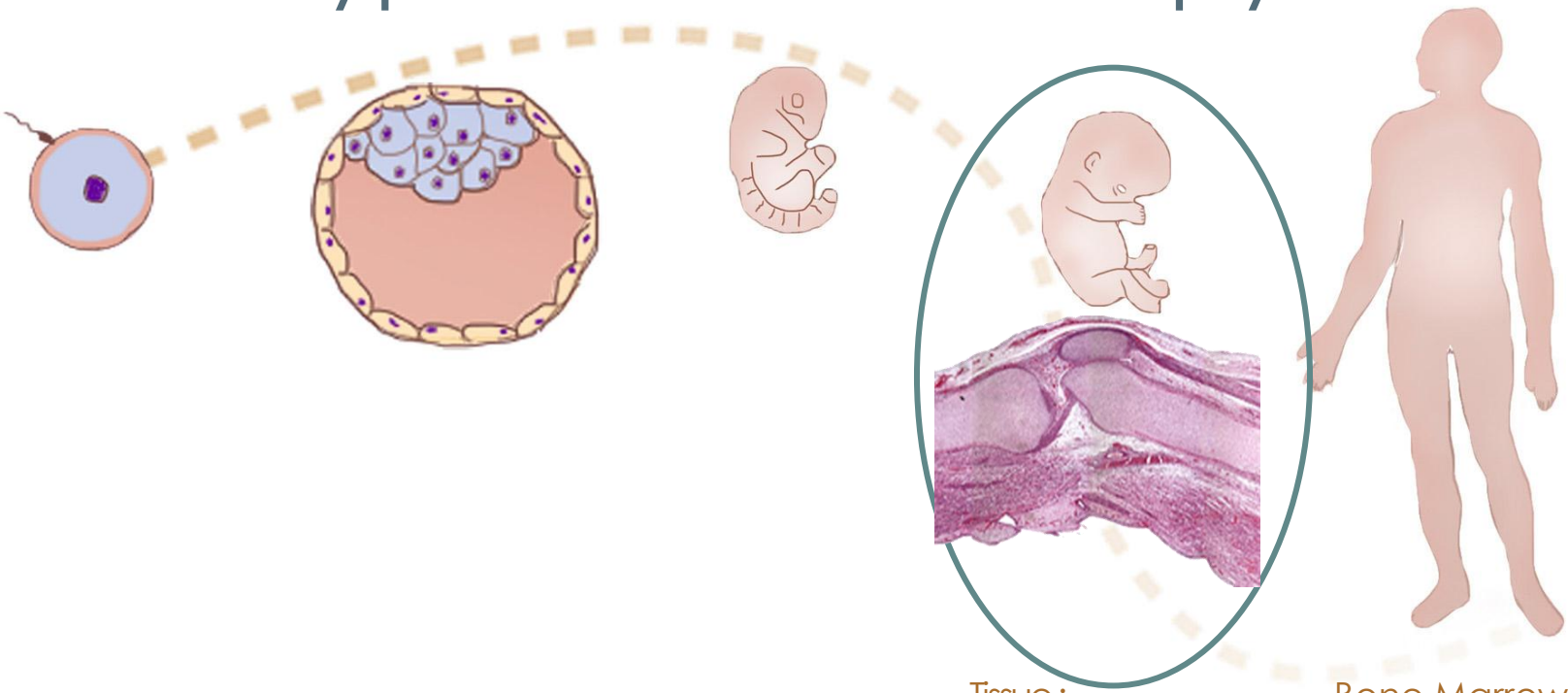




Adipose Stem Cells
3 weeks

Cells Types for Cell Therapy

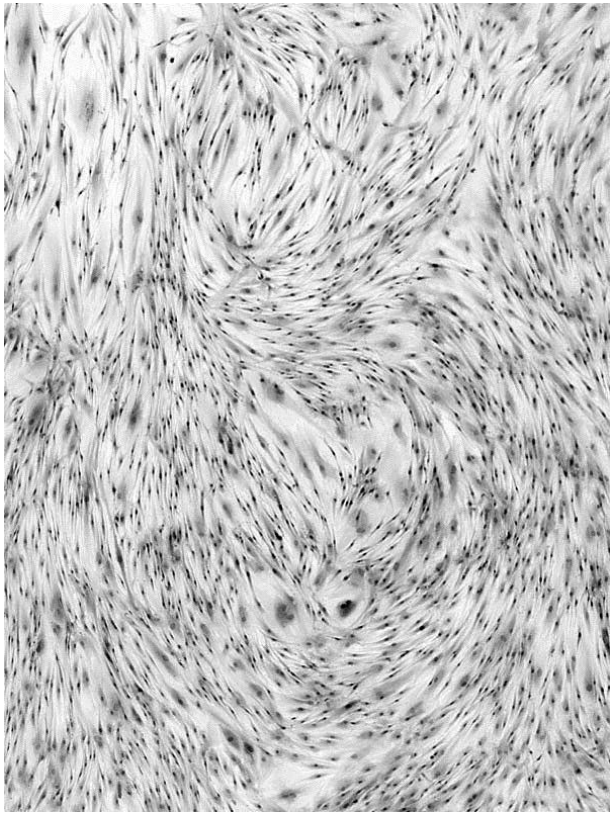


Inner cell mass from blastocyst	Genital ridge cells	Tissue : Skin, Bone Cartilage Specific cells	Bone Marrow, Adipose, Skin, Liver. 1 cell / 10^{4-5} cells
Embryonic Stem 0-2 weeks	Embryonic Fetal 5-8 weeks	Fetal Progenitor 9-14 weeks	Adult Specific or Stem

Fed. Licence

Organ donation

Fetal Progenitor Cells
Historical use



1930 Polio Vaccine

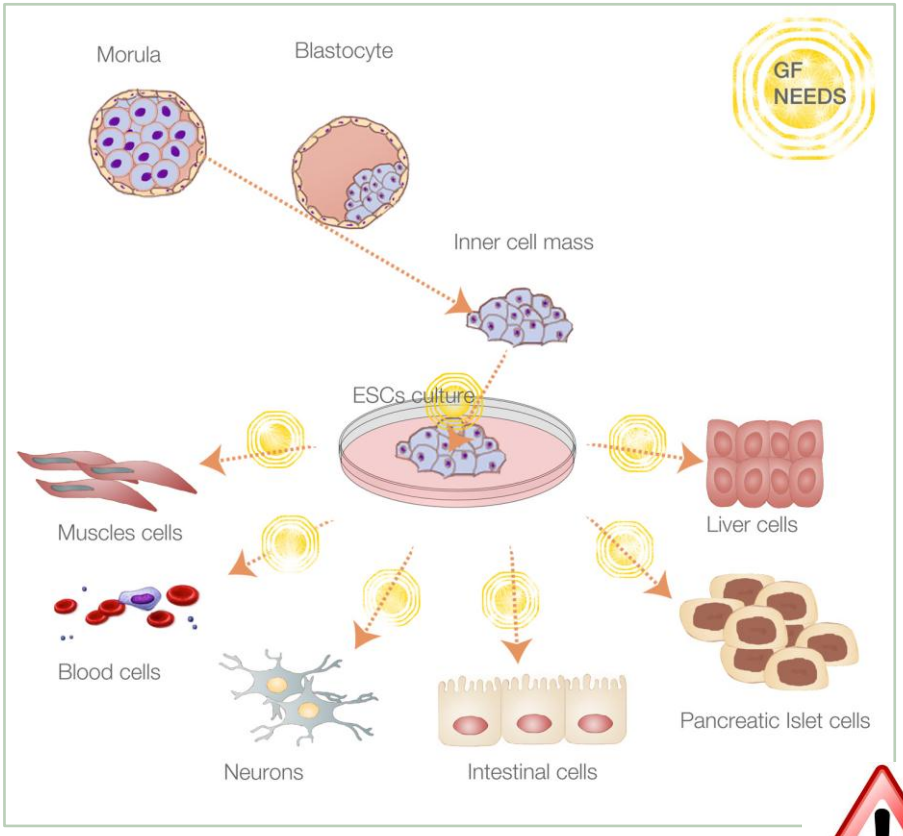
1954 Nobel Prize of medicine

1964-66 Until today

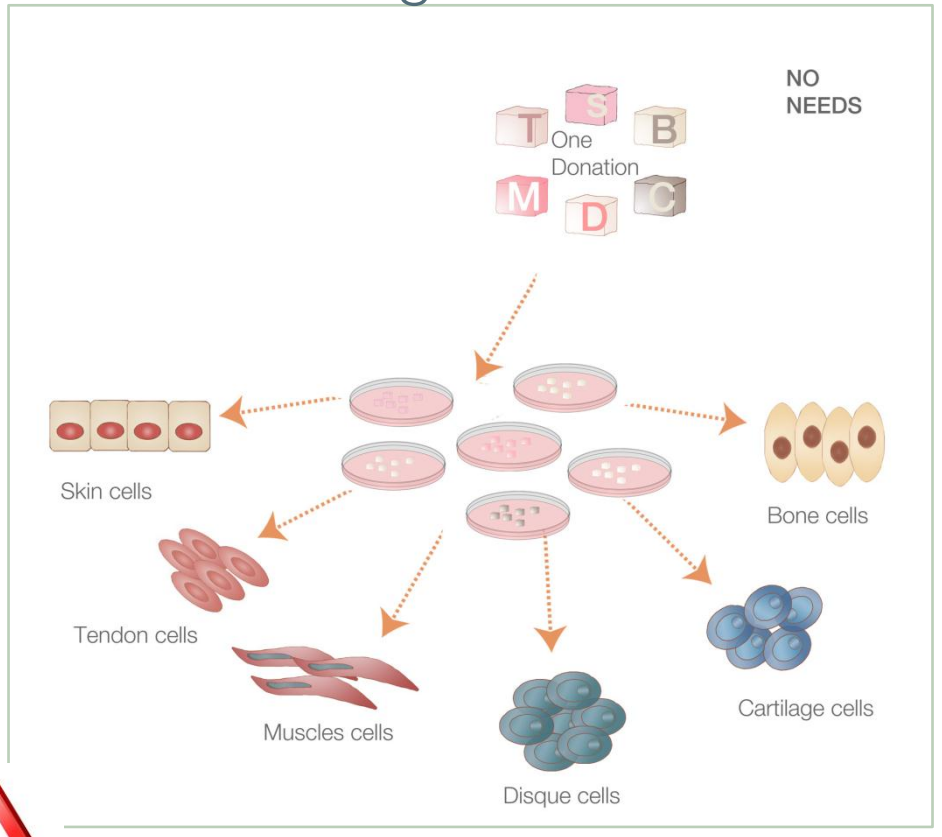
- Fetal Cells MRC-5 :
  polio, hepatitis A, chicken pox, measles, rabies
- Fetal Cells WI-38 :
  mumps vaccine [RA 27/3]

Progenitor Cells vs Stem cells

Stem cells

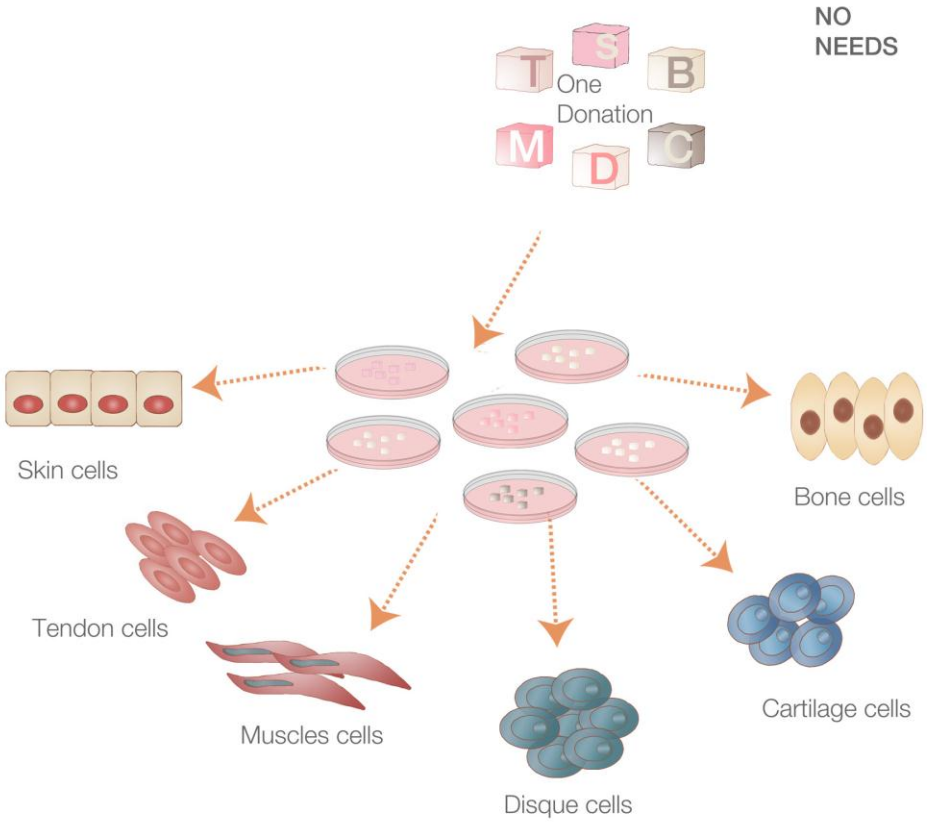


Progenitor cells



Not the same

Fetal Progenitor Cells



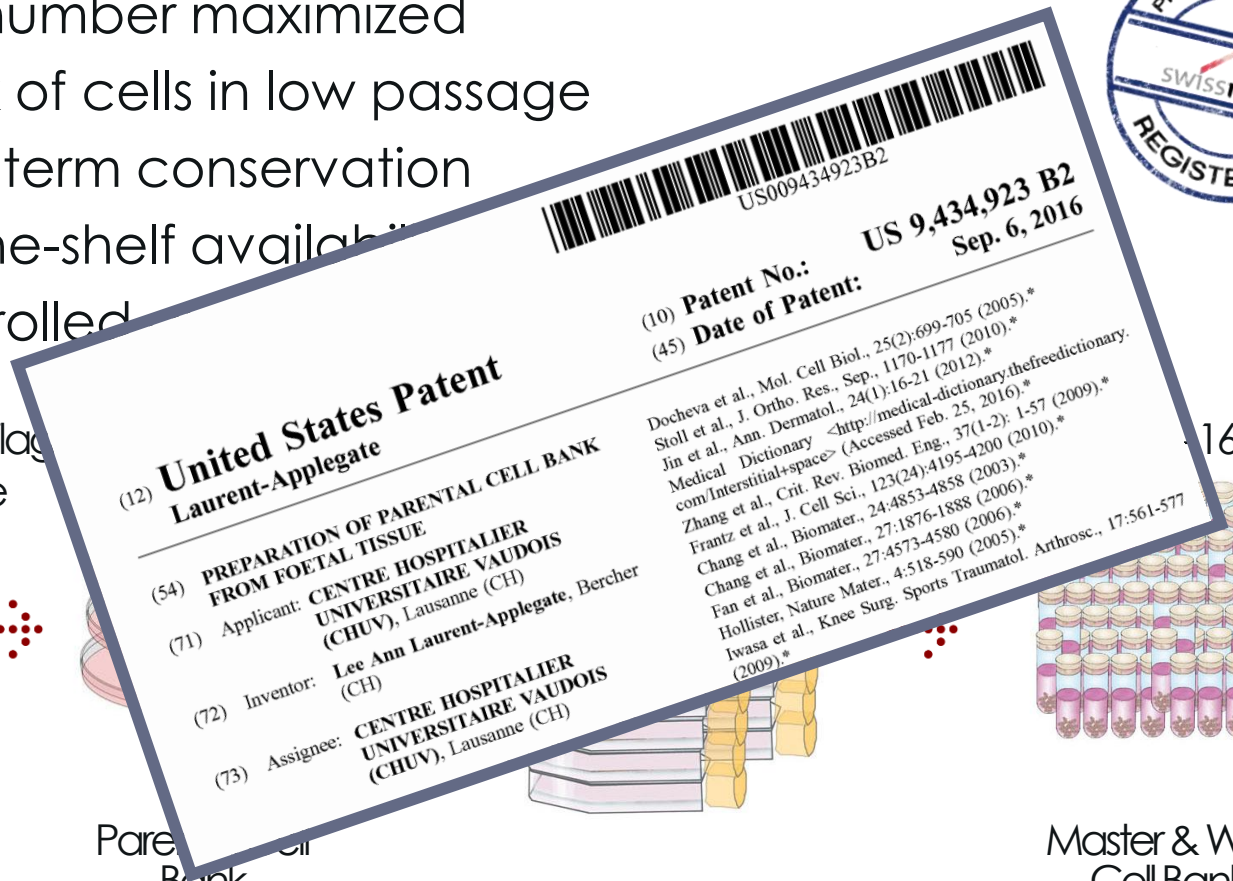
- Differentiated Cells
  - No specific growth factor needed
- Specific cell banks
  - Registration with OFSP/Swissmedic since 1993
  - Accordance with Transplantation Act [July 2007]
  - GMP quality
  - Compatibility with clinics
- High proliferation
- Long experience
- Scarless healing[1,2]

1. Bullard KM *et al.*, Fetal wound healing: current biology. World J Surg (2003)
2. Beredjiklian *et al.*, Regenerative versus reparative healing in tendon. Ann Biomed Eng (2003)

Creation of a cell bank [1993]

Cell bank

- Cell number maximized
- Stock of cells in low passage
- Long term conservation
- Off-the-shelf availabi
- Controlled



Progenitor cell bank
swissmedic
REGISTERED

Skin, Bone, Cartilag
Tendon, Muscle

-165°C

Biopsy

Pare
Bank
[PCB]

Cell Amplification

Master & Work
Cell Bank
[MCB & WCB]

Lausanne trial 2000-2005
Biologic bandages

Treatment of burns and wounds

Cell Bank 165°C

9 x 12 Constructs

Application

Optimization of Biobank:

35,000,000,000 constructs [9 x 12 cm]

Trial on 8 pediatric burns
10 year Follow-up

Dr. de Buys Roessingh

J Hohlfeld, AS de Buys Roessingh, C Scaletta, N Burri, P Hohlfeld, and LA Applegate
The Lancet, 366 :840-842, 2005

Biologic bandages

Tissue engineered fetal skin constructs for paediatric burns

Judith Hohlfeld, Anthony de Buys Roessingh, Nathalie Hirt-Burri, Pascal Chaubert, Stefan Gerber, Corinne Scaletta, Patrick Hohlfeld, Lee Ann Applegate

Cell Transplantation, Vol. 15, pp. 823–834, 2006
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Development, Characterization, and Use of a Fetal Skin Cell Bank for Tissue Engineering in Wound Healing

Anthony S. De Buys Roessingh,* Judith Hohlfeld,* Corinne Scaletta,† Nathalie Hirt-Burri,* Stefan Gerber,‡ Patrick Hohlfeld,‡ Jan-Olaf Gebbers,§ and Lee Ann Applegate†

Skin Pharmacology and Physiology

Skin Pharmacol Physiol 2009;22:63–73
DOI: 10.1159/000178865

Published online: February 4, 2009

Whole-Cell Bioprocessing of Human Fetal Cells for Tissue Engineering of Skin

L.A. Applegate[a, c] C. Scaletta[a, c] N. Hirt-Burri[a] W. Raffoul[b] D. Pioletti[c]

Experimental Gerontology 44 (2009) 208–218

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

ELSEVIER

Chronic wound healing by fetal cell therapy may be explained by differential gene profiling observed in fetal versus old skin cells

Albert-Adrien Ramelet[b,2], Nathalie Hirt-Burri[a,1,2], Wassim Raffoul[f], Corinne Scaletta[a,e], Dominique P. Pioletti[d,e], Elizabeth Offord[c], Robert Mansourian[c], Lee Ann Applegate[a,e,*]

Roessingh et al., J Regen Med 2015, 4:1
http://dx.doi.org/10.4172/2325-9620.1000122

Journal of Regenerative Medicine

A Decade after Foetal Skin Progenitor Cell Therapy in Pediatric Burn Treatment

Anthony de Buys Roessingh[2], Nathalie Hirt-Burri[1], Wassim Raffoul[1], Corinne Scaletta[1] and Lee Ann Applegate[1*]

- Not a graft
- Activate the regeneration of tissue
- Stimulate the closure of burns/wounds
- Reduced hypertrophic scar
- Presence of sebaceous glands and hair follicles
- Excellent mobility results [10 year follow-up]

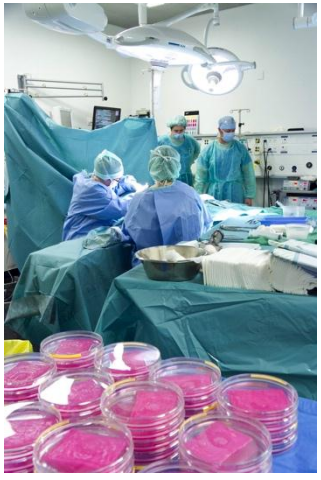
Severe burns: actual care 12% TBSA Day 2

Severe burns: actual care 12% TBSA Day 4

Severe burns: actual care 12% TBSA 6 weeks

Treatments with progenitor cells

- Cadaver skin replacement
- Preparation of graft sites
- Treatment of donor graft sites
  - Formulation and delivery
- Stimulation of mesh grafts « sandwich technique »



Cell therapies – Co-cultures are the future!

- Necessary for epidermal cover
- Role in optimal reconstruction of skin
- Role in soft tissue and appendix reconstruction
  - Hair follicles
  - Sebaceous glands
  - Nerves
  - …

From the laboratory to clinical research and use…

1987

First autologous cell therapies

1991-2005

Development Swiss Transplantation Program
&
Clinical Research – allogenic cell therapies

2007

New Regulations for ATMP
&
Re-registration of Swiss Transplantation Program

2009

Transposition of procedures to Cell Production Center (GMP)

2015

License for cell production SwissMedic
&
Burn Center accreditation (EBA)

2017-2018

Routine Integration of innovative cell therapies in patient care

Annals of Burns and Fire Disasters - vol. XXIX - n. 2 - June 2016

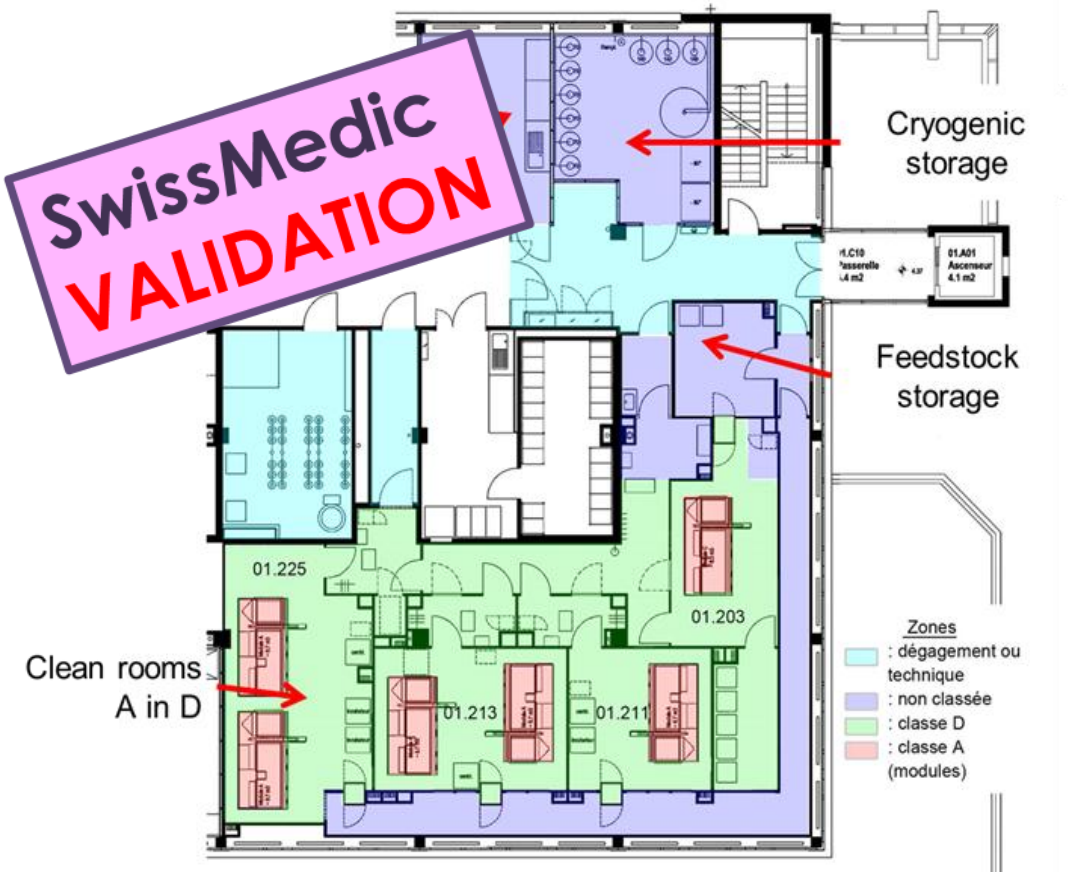
BURN PATIENT CARE LOST IN GOOD MANUFACTURING PRACTICES?

LA QUALITÉ DES SOINS AUX BRÛLÉS DISPARAÎTRA- ELLE AU PROFIT DES "BONNES PRATIQUES DE FABRICATION"?

Dimitropoulos G.,[1] Jafari P.,[1] de Buys Roessingh A.,[2] Hirt-Burri N.,[1] Raffoul W.,[1] Applegate L.A.[1]✉

[1] Plastic, Reconstructive & Hand Surgery, Unit of Regenerative Therapy, University Hospital of Lausanne, Switzerland
[2] Department of Pediatric Surgery, University Hospital of Lausanne, Switzerland

Cell Therapies infrastructure- GMP obligation



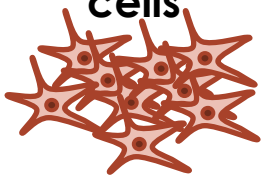
New Generation of Cell Therapy Formulations SwissTransMed 2014-2017 2 mio CHF

B5 PLATFORM
Bandages
Biologic
Biodegradable
anti-**B**acterial
For **B**urns

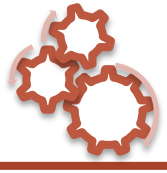
NEW FORMULATIONS

Cells

Progenitor skin cells



Transfection with antimicrobial peptides



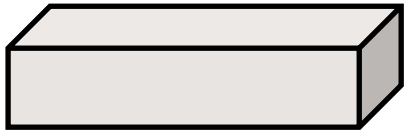
Scaffold

Collagen Matrix

TissuFleece®

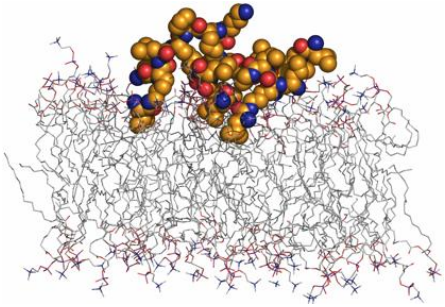
Baxter CE

Chitosan Matrix



Chitofoams

Integration of dendritic antimicrobial Peptides



Anti-Virulence = Anti-Quorum Sensing
Metal or Metal Chelators
Antibiotics

Projet SwissTransMed : B^5

Professeur
Wassim Raffoul
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HUG

Docteur
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swissuniversity.ch
CHUV

SwissTransMed 2014-2017

- Platform Cordinatrice: Dr. Paris Jafari

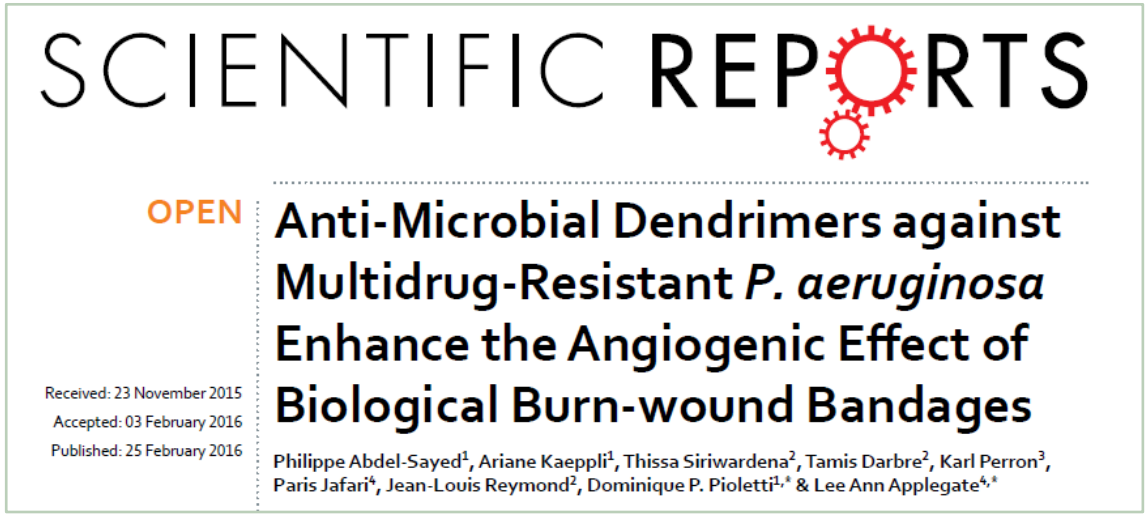
Translating Fundamental mechanisms to the clinic

First Formulation Chosen

- AMPDs might improve burn-wound healing by increasing **angiogenesis** and **cell migration** as characterized in vitro

Nature Scientific Reports : February 25, 2016 - online

Abdel-Sayed P, Kaeppli A, Siriwardena T, Darbre T, Perron K, Jafari P, Reymond J-L, Pioletti D, Applegate LA



SCIENTIFIC REPORTS

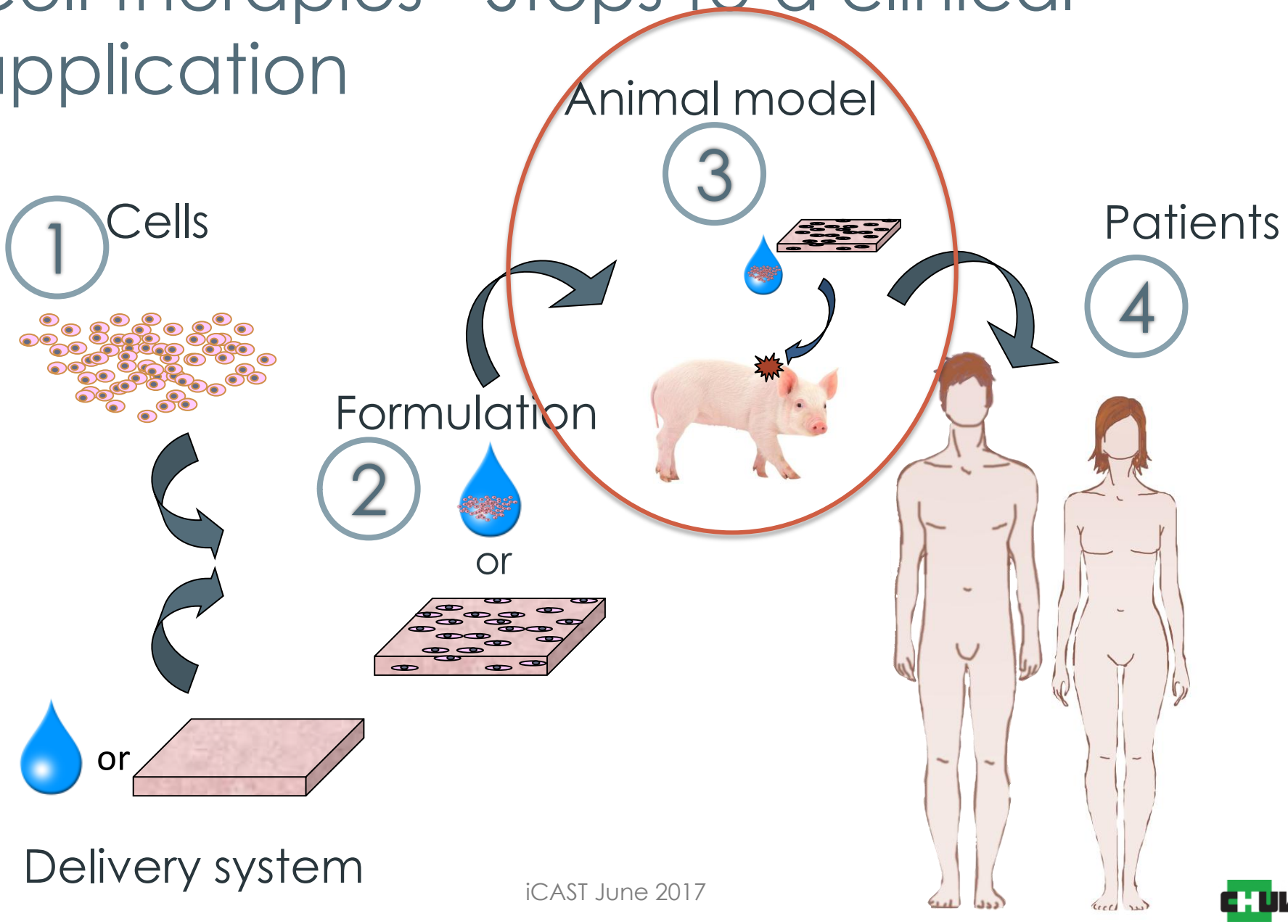
OPEN

Anti-Microbial Dendrimers against Multidrug-Resistant *P. aeruginosa* Enhance the Angiogenic Effect of Biological Burn-wound Bandages

Received: 23 November 2015
Accepted: 03 February 2016
Published: 25 February 2016

Philippe Abdel-Sayed[1], Ariane Kaeppli[1], Thissa Siriwardena[2], Tamis Darbre[2], Karl Perron[3], Paris Jafari[4], Jean-Louis Reymond[2], Dominique P. Pioletti[1,*] & Lee Ann Applegate[4,*]

Cell therapies - Steps to a clinical application



Thank you for your attention!

IN MEMORIAL of Sir Roger Moore
He & Lady Kristina: Godparents of Applegate Lab

SwissTransMed Platforms for Translational Research in Medicine

Foundation S.A.N.T.E.

HO
Fondation de soutien à la recherche dans le domaine de l'orthopédie - traumatologie

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SANDOZ-FONDATION DE FAMILLE

European Commission
Seventh Framework Programme (FP7)

canton de vaud

iCAST June 2017

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