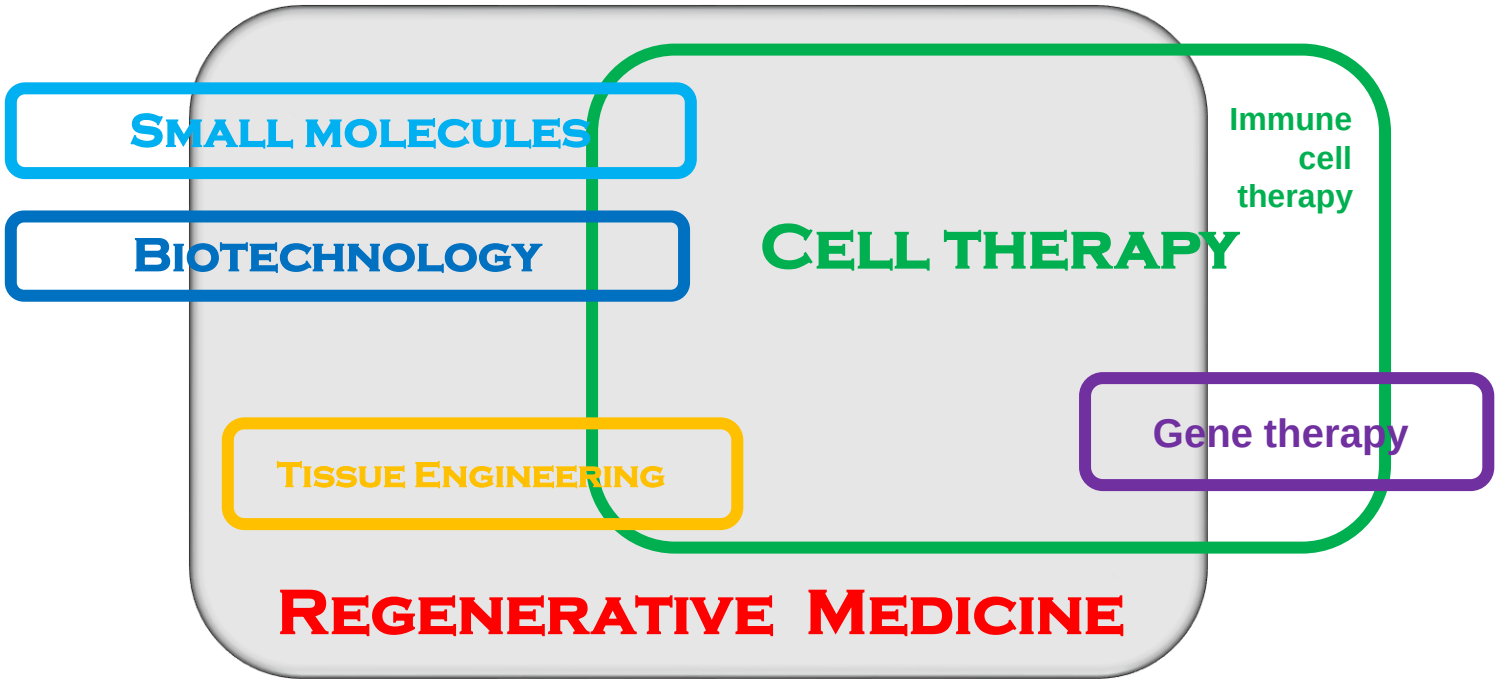
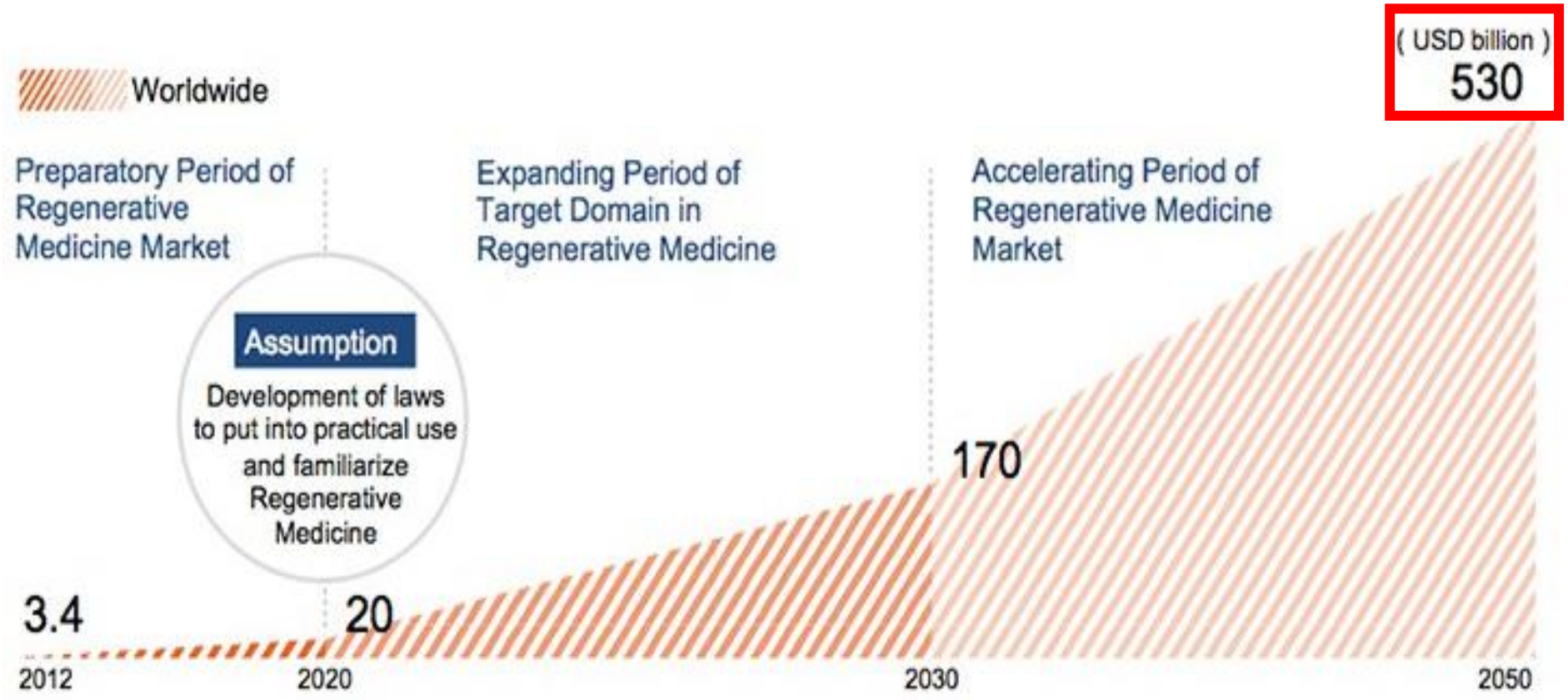
Regenerative Medicine in Skin Diseases

Amir Bajouri, MD

Regenerative Medicine Department, Royan Institute

Regenerative medicine field




(USD billion)
530
Worldwide
Preparatory Period of Regenerative Medicine Market
Expanding Period of Target Domain in Regenerative Medicine
Accelerating Period of Regenerative Medicine Market
Assumption
Development of laws to put into practical use and familiarize Regenerative Medicine
170
3.4
20
2012
2020
2030
2050

Time's hottest jobs of the future

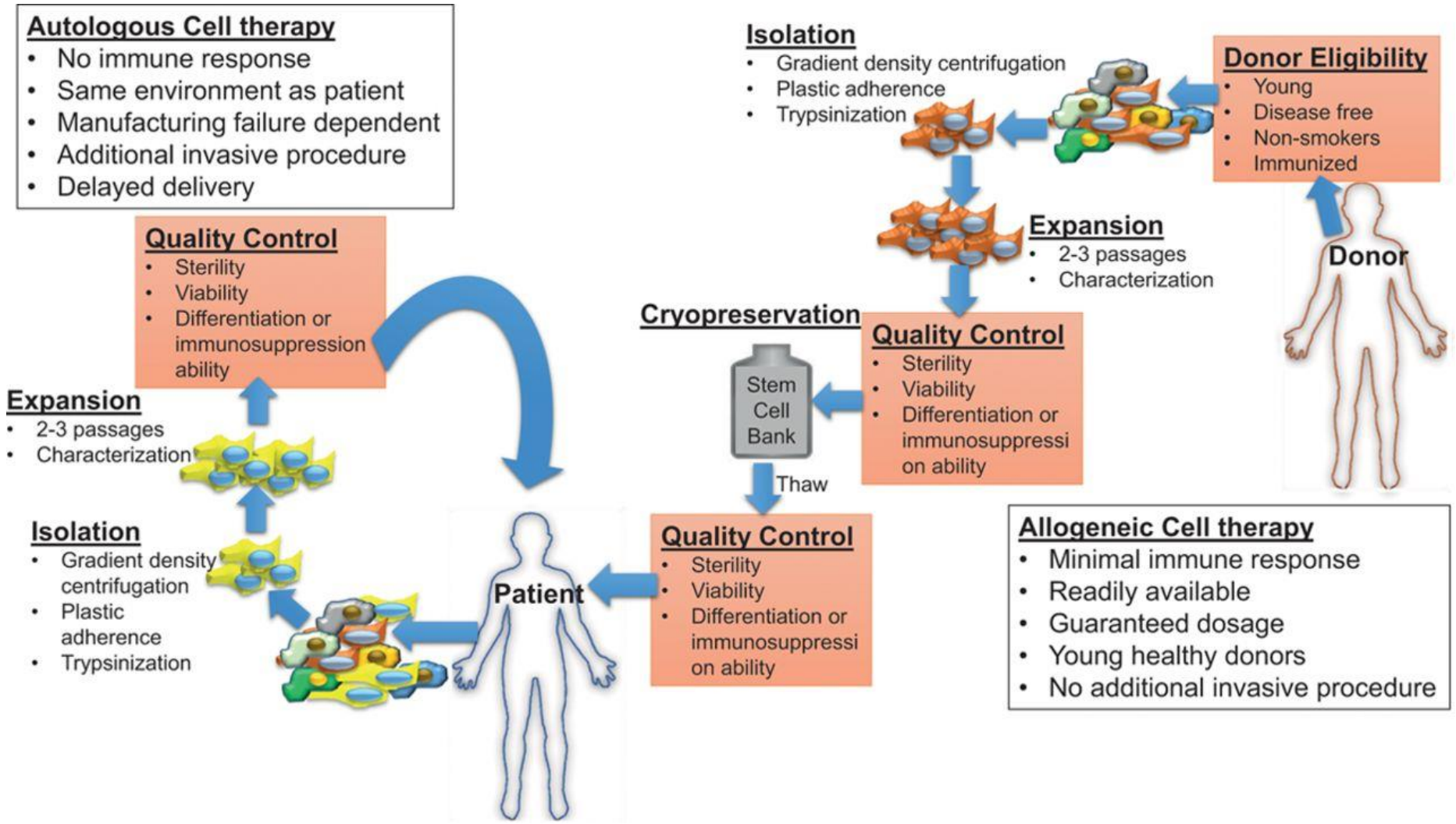
1. Tissue engineers
2. Gene programmers
3. Pharmers
4. Frankenfood monitors
5. Data miners

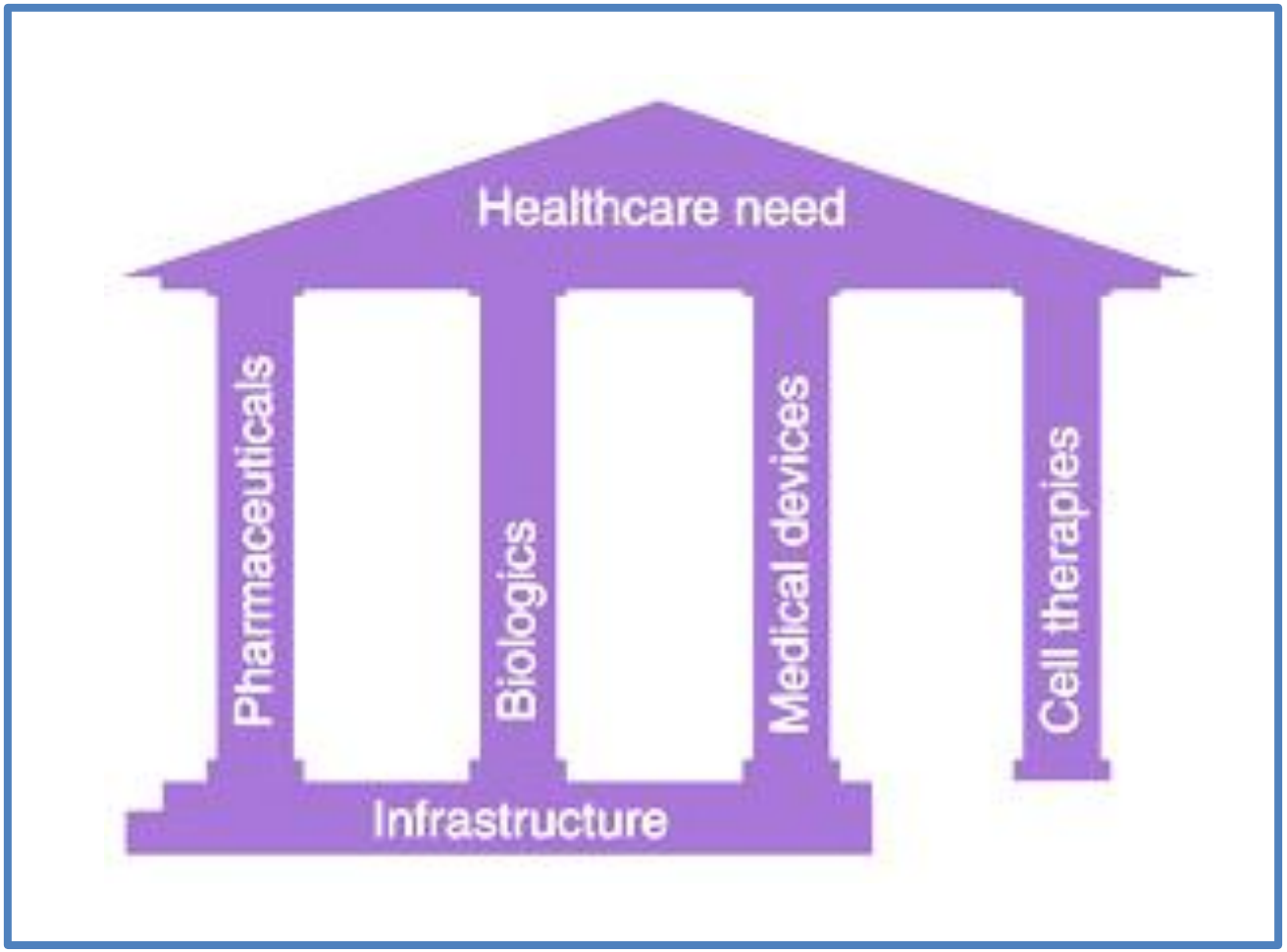
Cell therapy:

Administration to humans of autologous, allogeneic, or xenogeneic living cells which have been manipulated or processed ex vivo

Autologous

Allogeneic

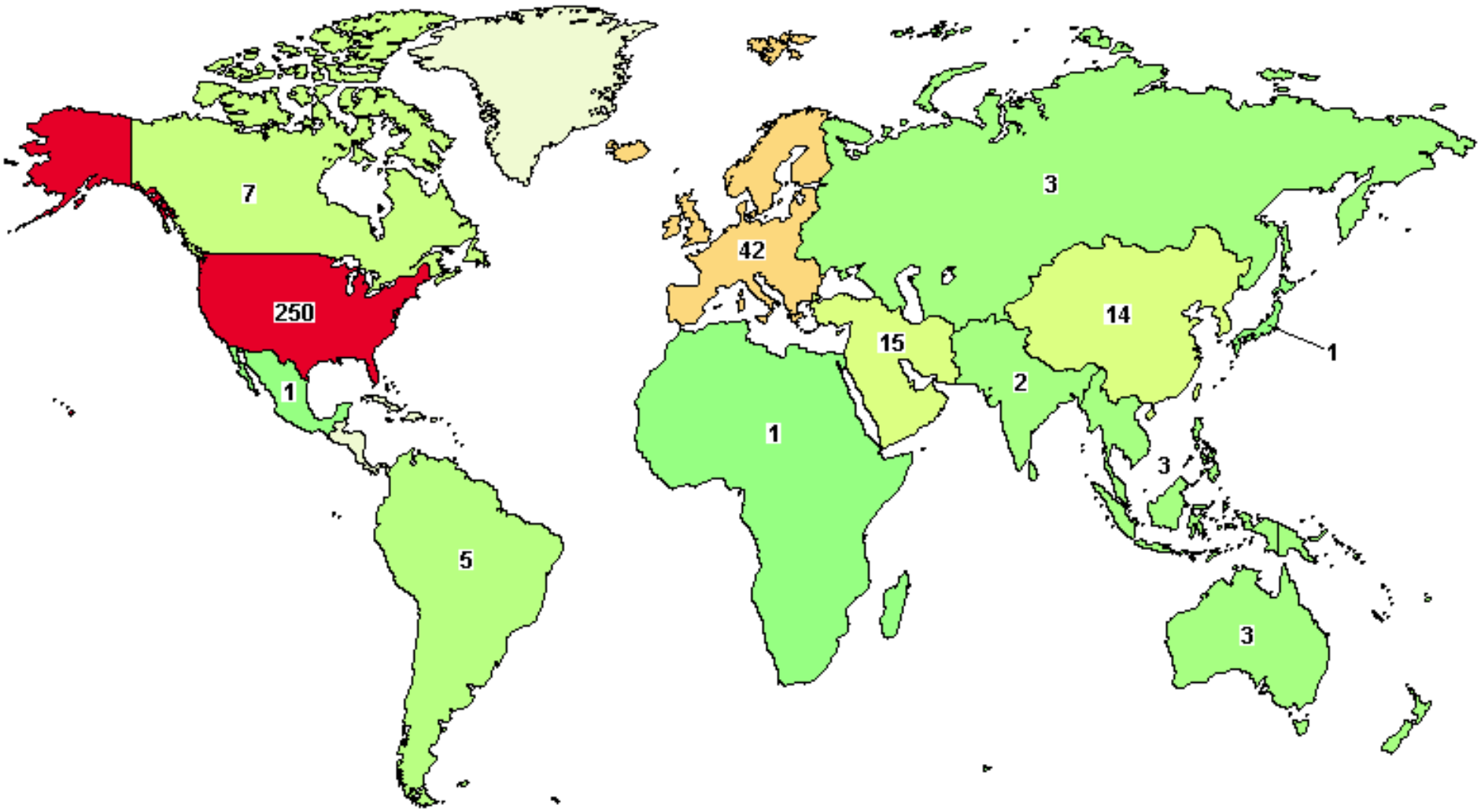




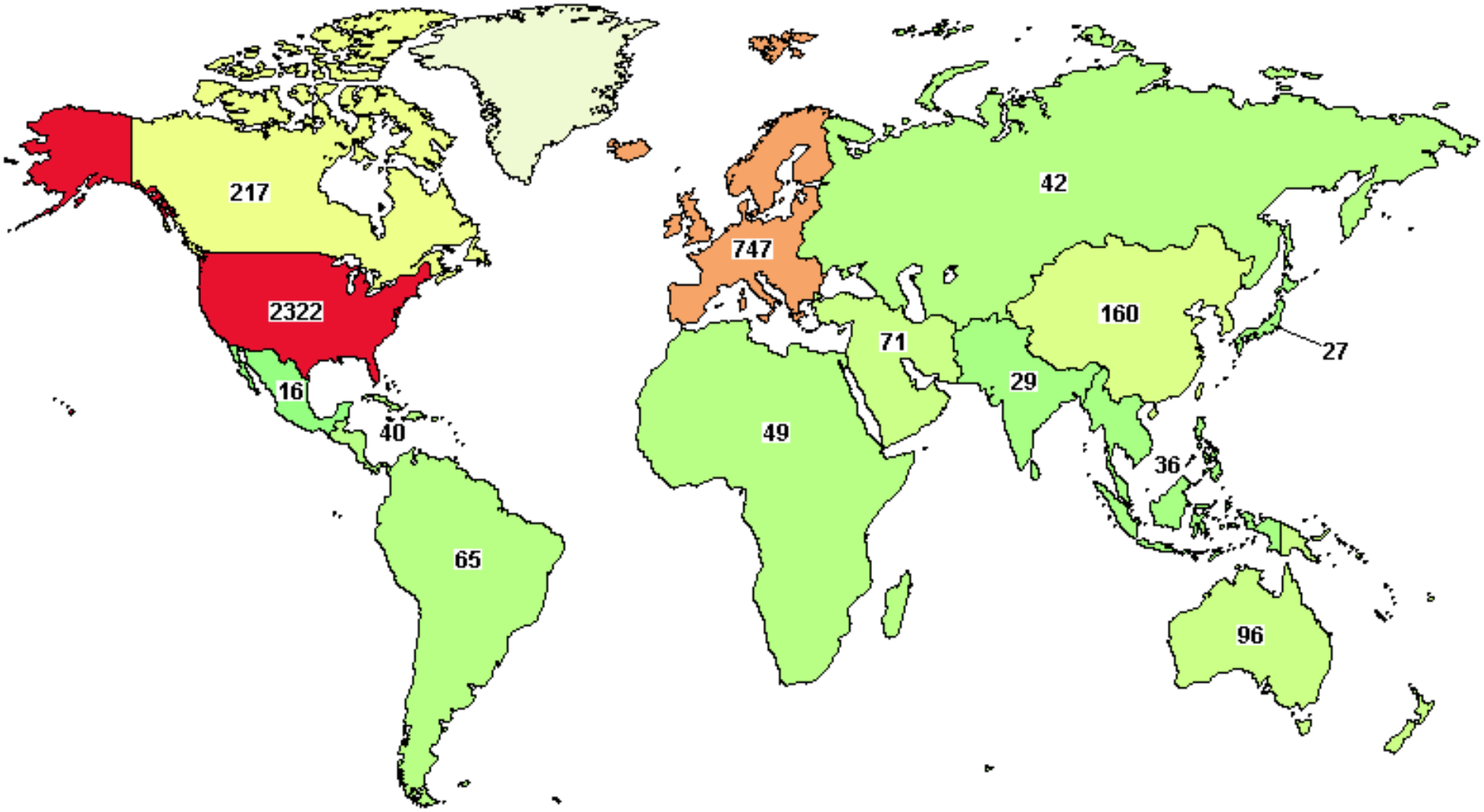
Two decades ago, the pharmaceutical industry—long dominated by small-molecule drugs—was revolutionized by the advent of biologics. Today, biomedicine sits on the cusp of a new revolution: the use of human cells as versatile therapeutics.

Overall	Cell therapy	Cell therapy in skin
• **229,810**	• **34,406 (15%)**	• **3,678 (10%)**

Cell therapy in skin diseases- 2014



Cell therapy in skin diseases- 2016



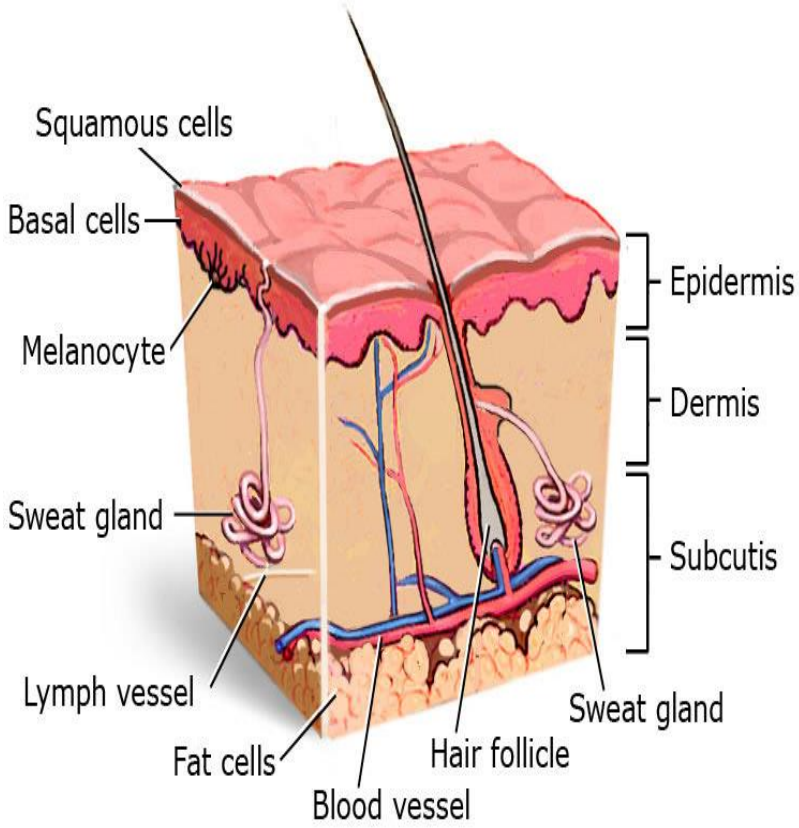
Royan Cell Therapy Center

Skin Clinic

- Established: 2007
- Number of patients annually: around 300
- Till now: more than 2500 patients

Skin

- Biggest organ of the body
- 8% of body weight



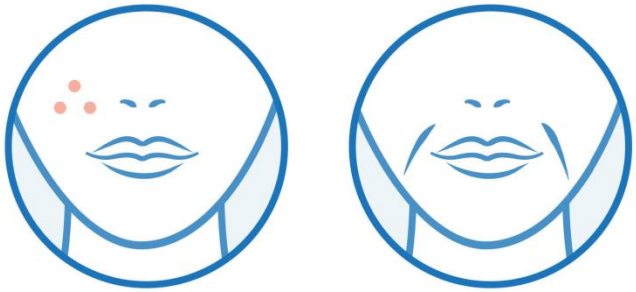
Functions:

- Appearance, Quality of Life
- Barrier function
- Immunologic function
- Temperature regulation
- Photo protection/ vitamin D synthesis
- Nerve sensation
- Wound healing

Cell Therapy in Skin Diseases

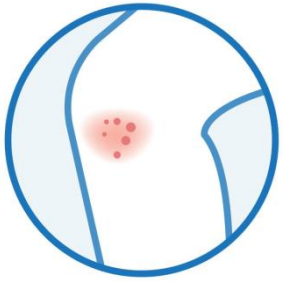
Aesthetic medicine

Wrinkle, Acne scar

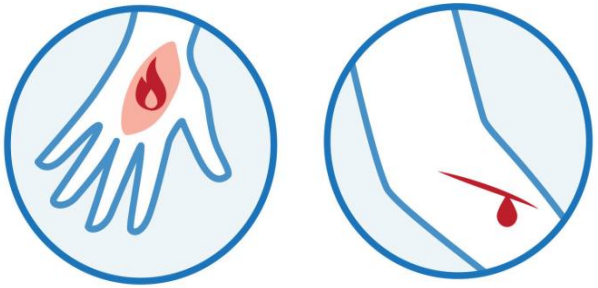


Autoimmune diseases

Vitiligo, Psoriasis, SLE, Scleroderma



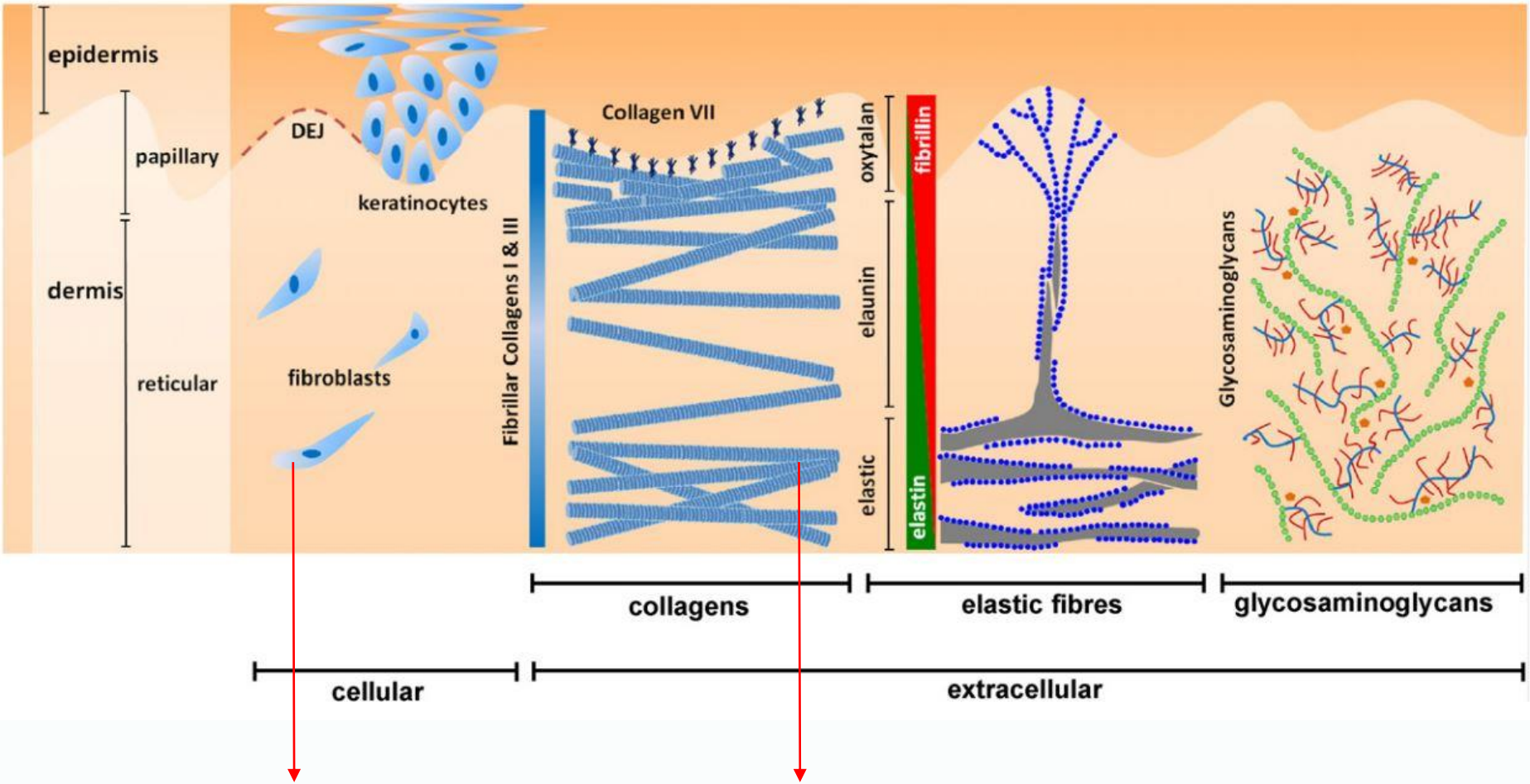
Burns and wounds



Skin Rejuvenation

Aging is a process of progressive decrease in the functioning and reserve capacity of all organs in the body, including skin

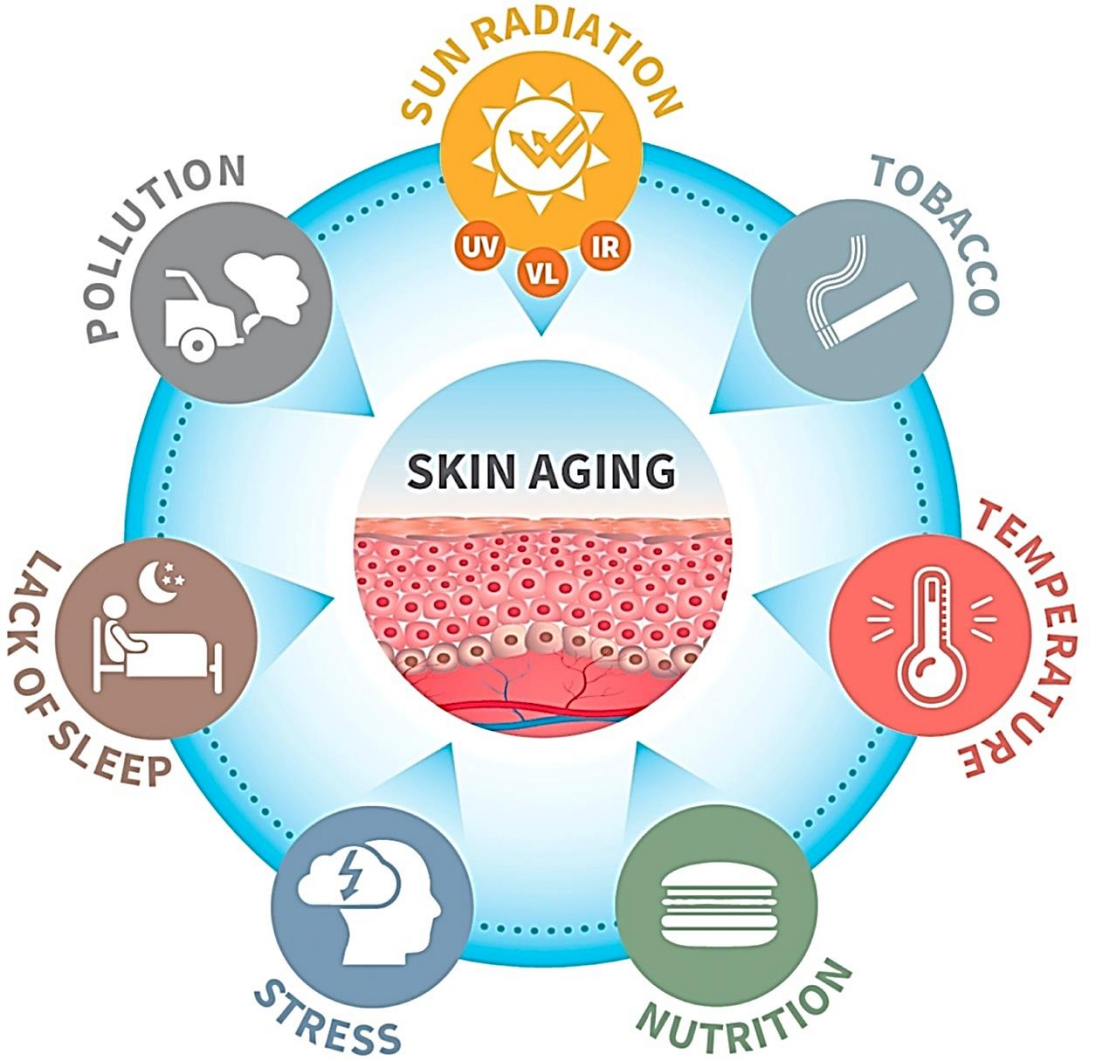
Normal Skin Structure



Main cells of dermal layer

Main component of ECM

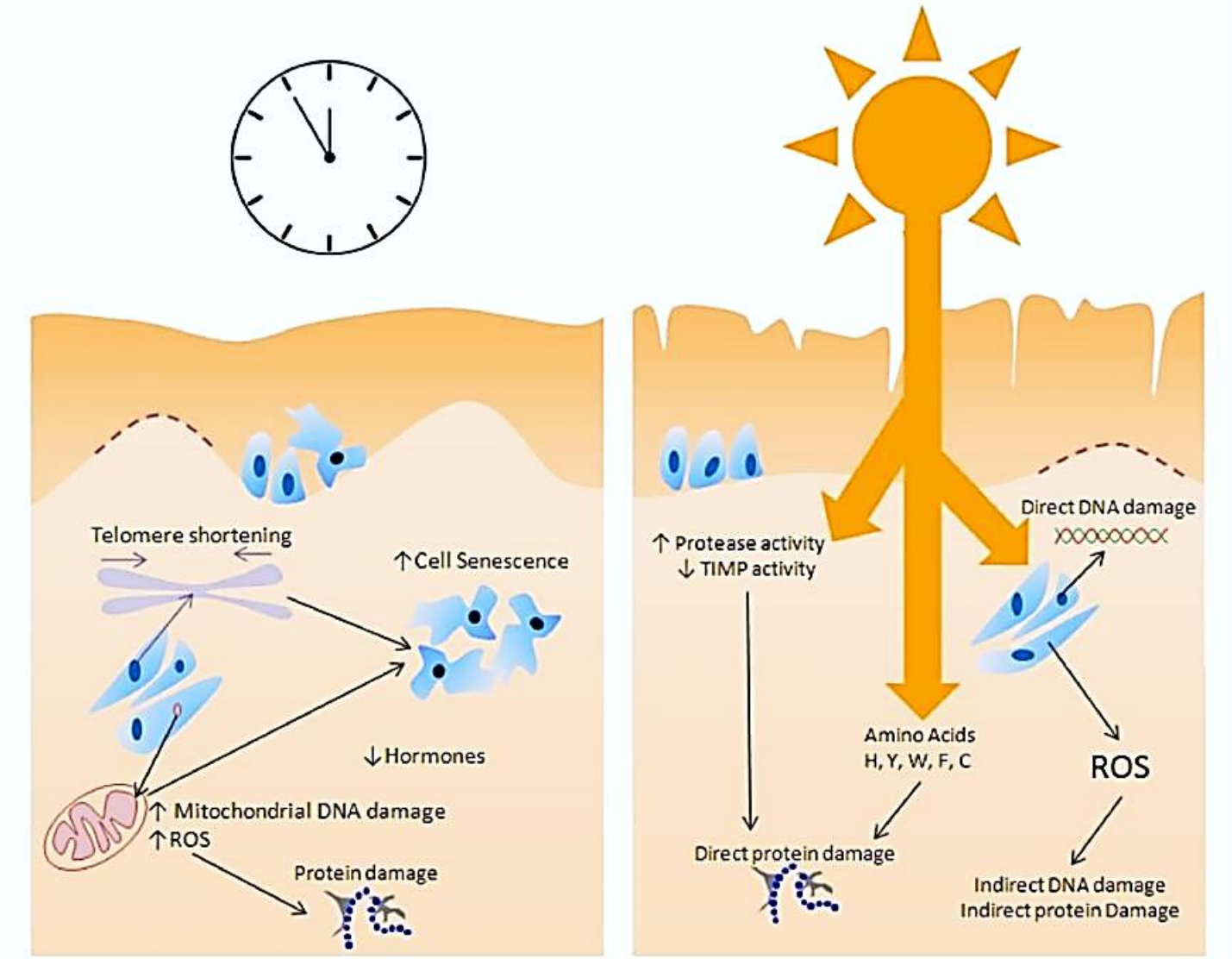
Skin Ageing Factors



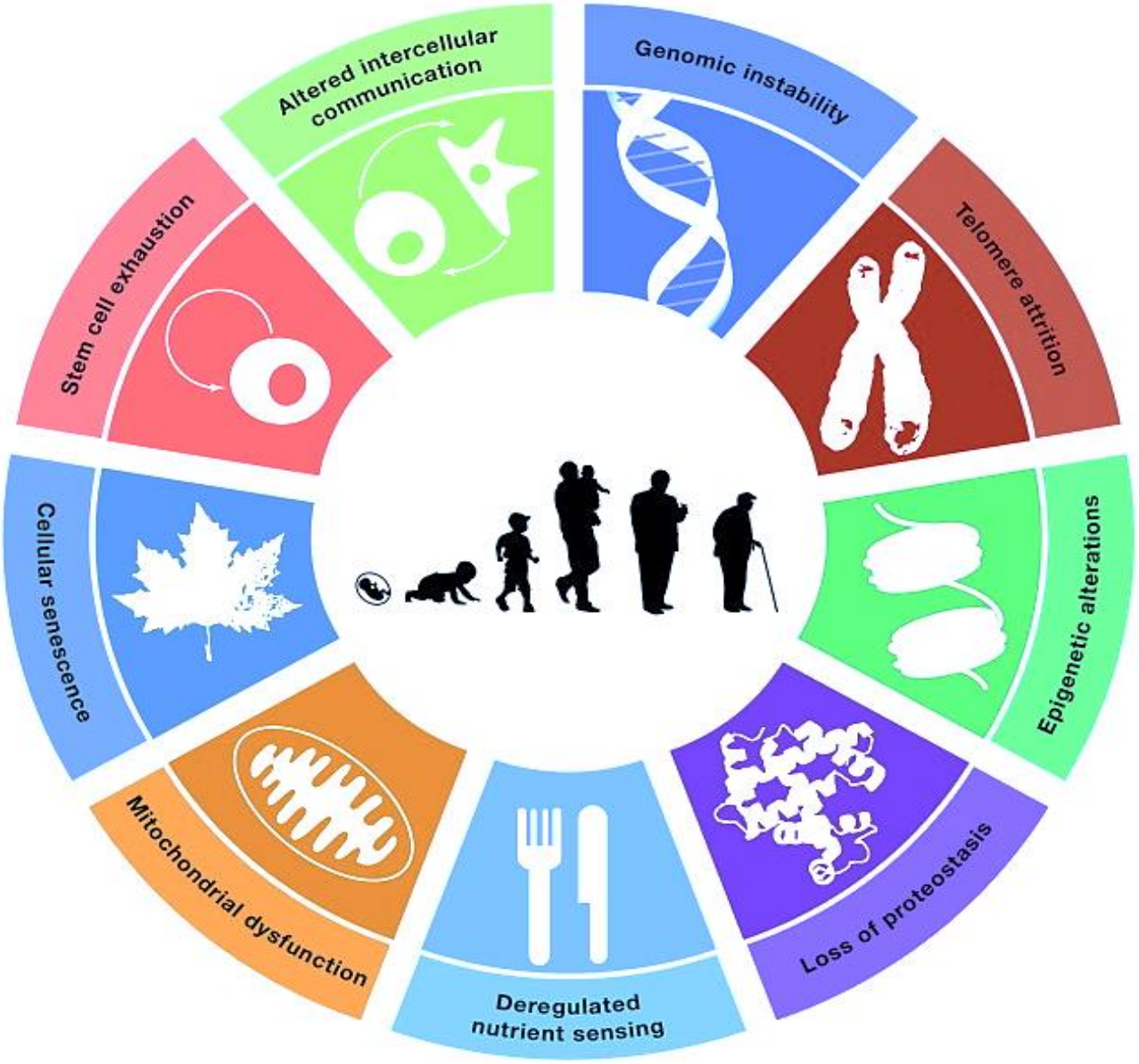
Ageing Pathways

Intrinsic

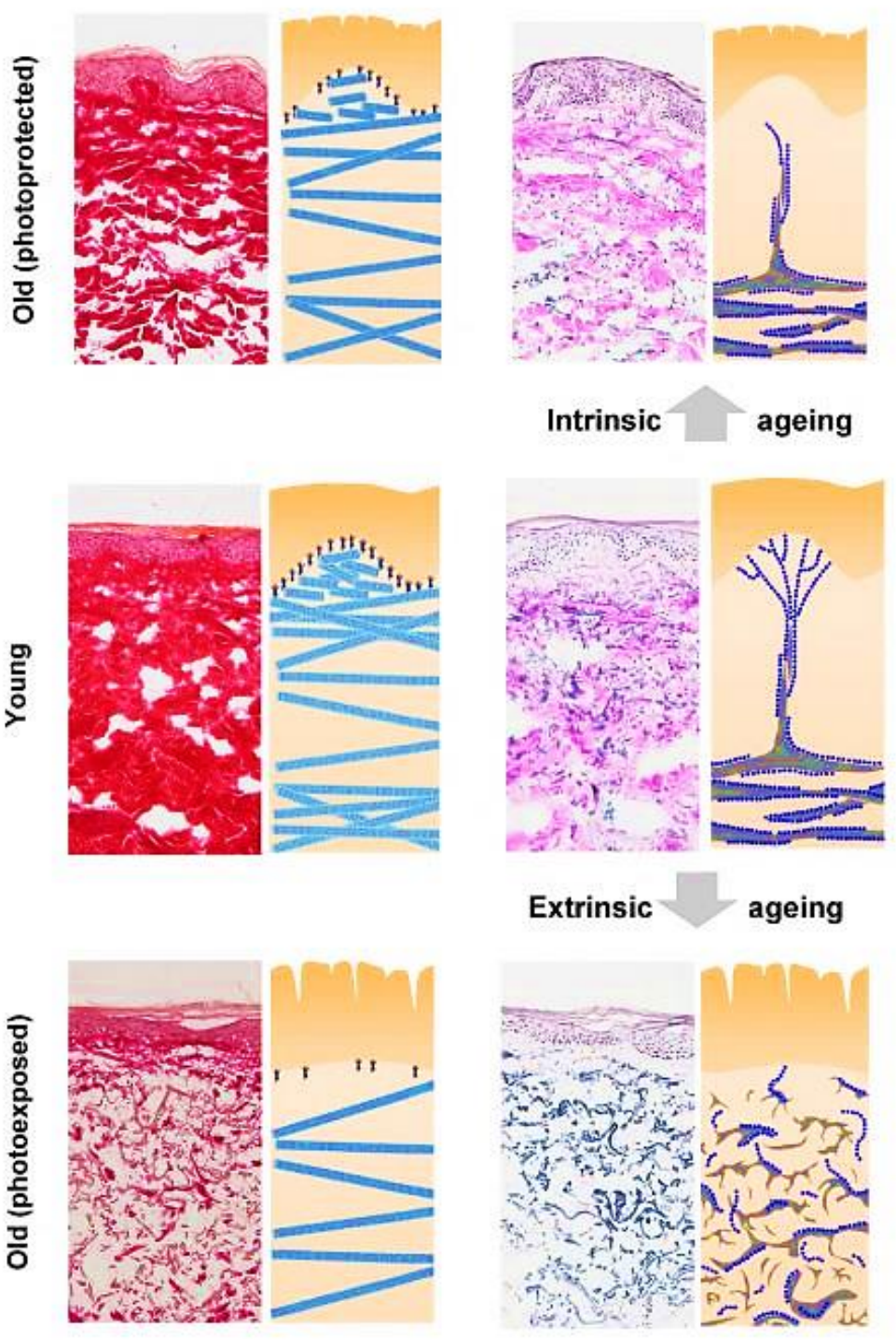
Extrinsic



Mechanisms of Intrinsic Ageing



- Flattening of dermal- epidermal junction
- Loss of extracellular matrix
- Loss of vascular network and capillary loops
- Loss in size, amount, and potency of fibroblasts



History of Aesthetic Injectables

1800	Chemical agents
1893	Autologous fat
1950	Paraffin
1960	Liquid Silicon
1970	Bovine collagen
1981	Bovine collagen was approved by FDA
1989	Botulinum toxin
1990	Autologous human collagen
1992	Autologous fibroblast
2000	Hyaluronic acid
2011	Autologous Fibroblast was approved by FDA

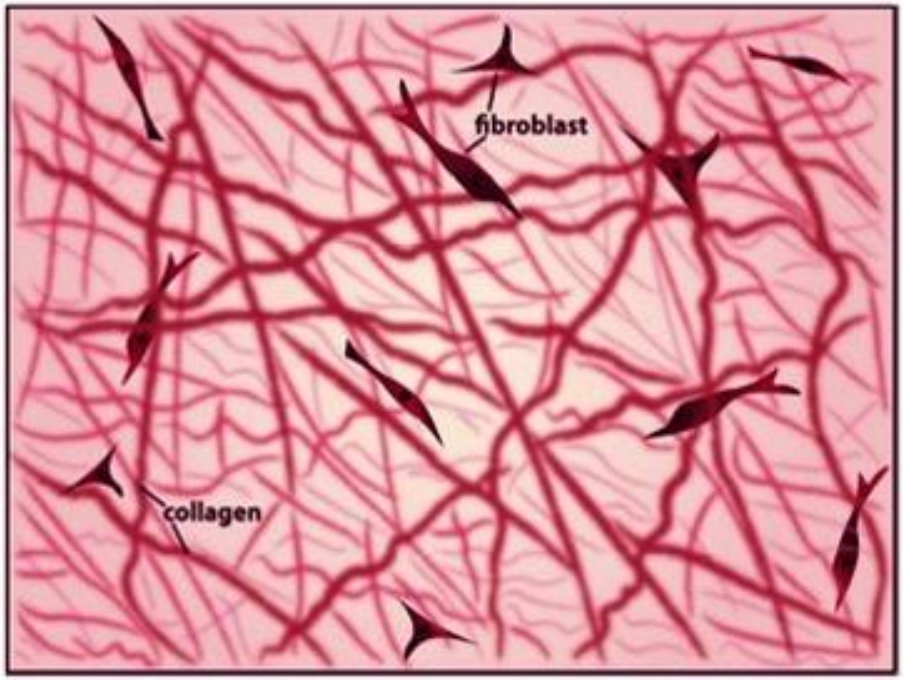
Autologous Fibroblast Transplantation

Skin sampling

- Cell cultivation
- 4-6 weeks

- 3 injections
- 3-5 weeks intervals
- 1–2 x 10^6 cells/cm

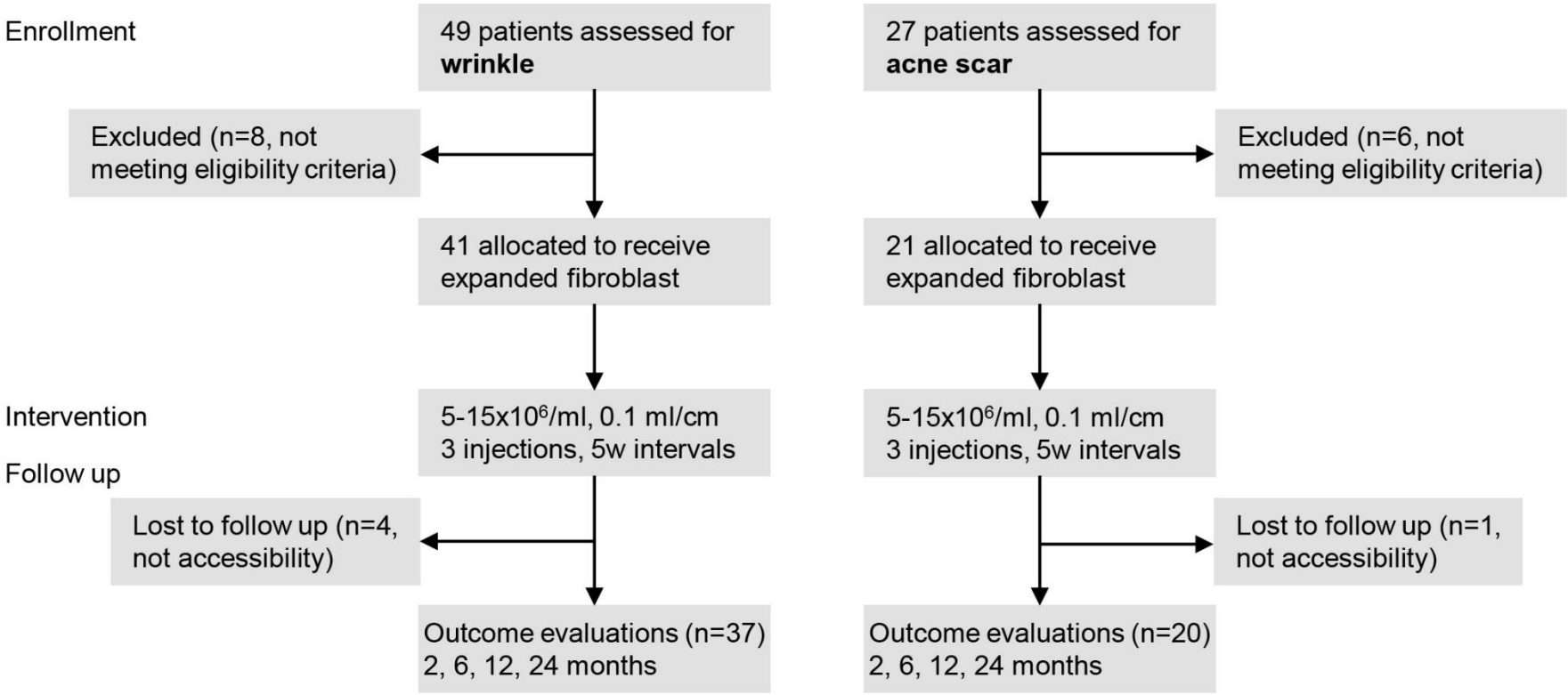
Why Fibroblast?

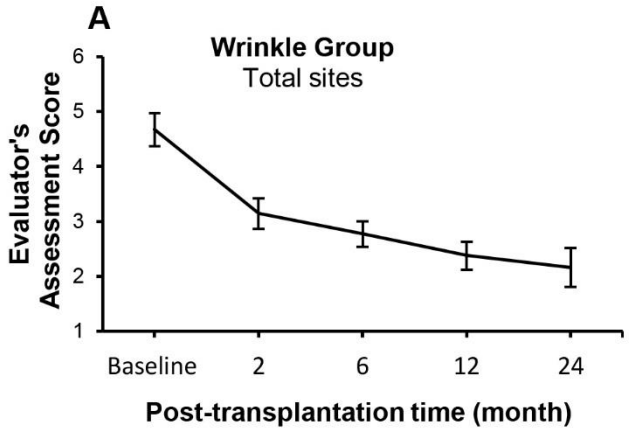


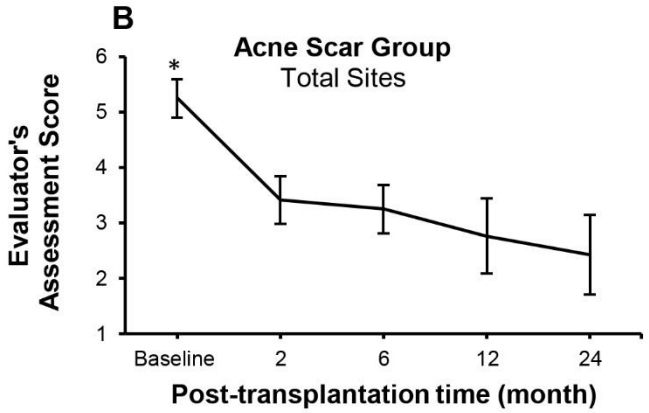
Dermal fibroblasts produce:

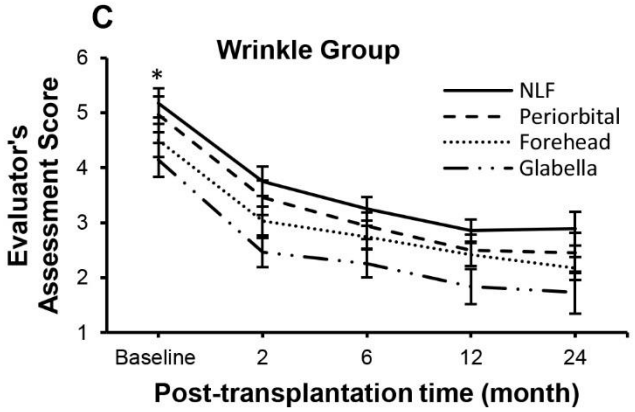
- Collagen type I
- Collagen type III
- Collagen type VII
- Elastin
- Hyaluronic acid (hyaluronin)
- Matrix metalloproteinases (MMPs)

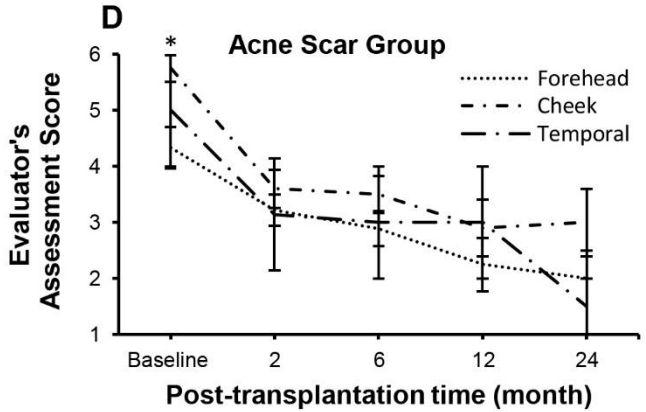
Royan Skin Clinic Experience

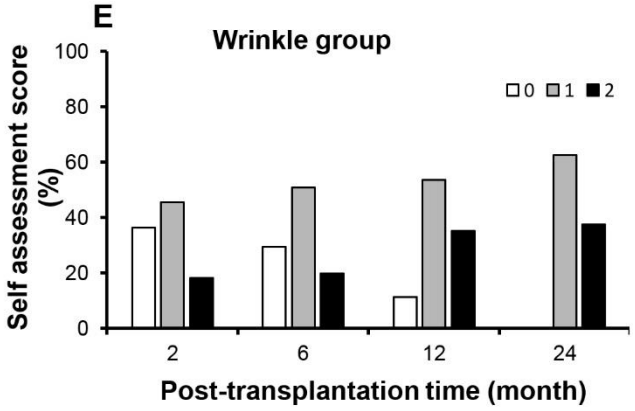


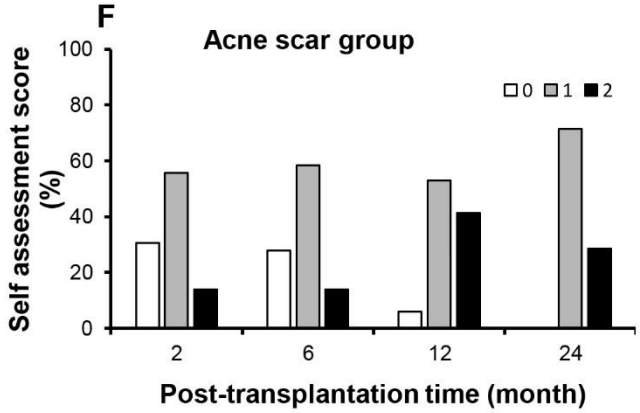

A
Wrinkle Group
Total sites
Evaluator's Assessment Score
6
5
4
3
2
1
Baseline
2
6
12
24
Post-transplantation time (month)


B
Acne Scar Group
Total Sites
*
Evaluator's Assessment Score
6
5
4
3
2
1
Baseline
2
6
12
24
Post-transplantation time (month)

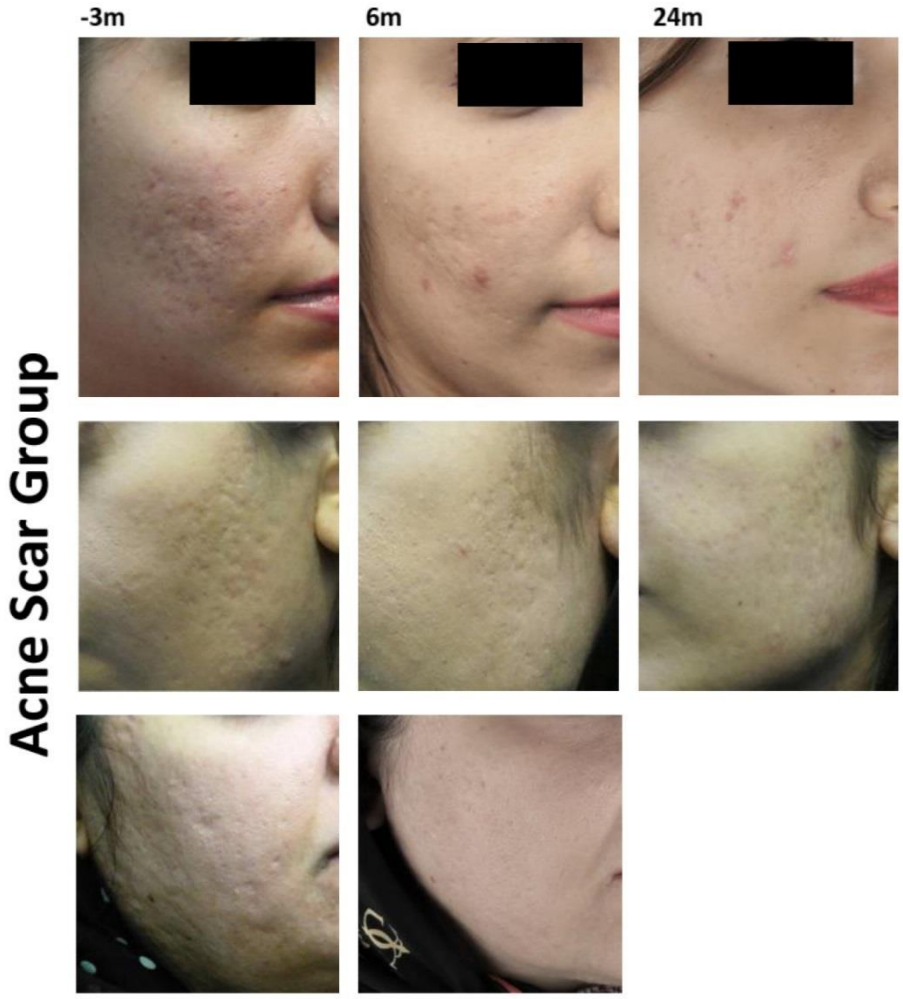

C
Wrinkle Group
*
NLF
Periorbital
Forehead
Glabella
Evaluator's Assessment Score
6
5
4
3
2
1
Baseline
2
6
12
24
Post-transplantation time (month)


D
Acne Scar Group
*
Forehead
Cheek
Temporal
Evaluator's Assessment Score
6
5
4
3
2
1
Baseline
2
6
12
24
Post-transplantation time (month)


E
Wrinkle group
0 1 2
Self assessment score (%)
100
80
60
40
20
0
2
6
12
24
Post-transplantation time (month)


F
Acne scar group
0 1 2
Self assessment score (%)
100
80
60
40
20
0
2
6
12
24
Post-transplantation time (month)


-3m
6m
24m
Wrinkle Group


-3m
6m
24m
Acne Scar Group

- **Filler's Disadvantages**

  - Rapid degradation
  - Granulomatous inflammation
  - Allergic reaction
  - Necrosis
  - Fibrosis
  - Abscess formation
  - Microcyst
  - Calcification
  - Infection

- **Autologous Fibroblast Benefits**

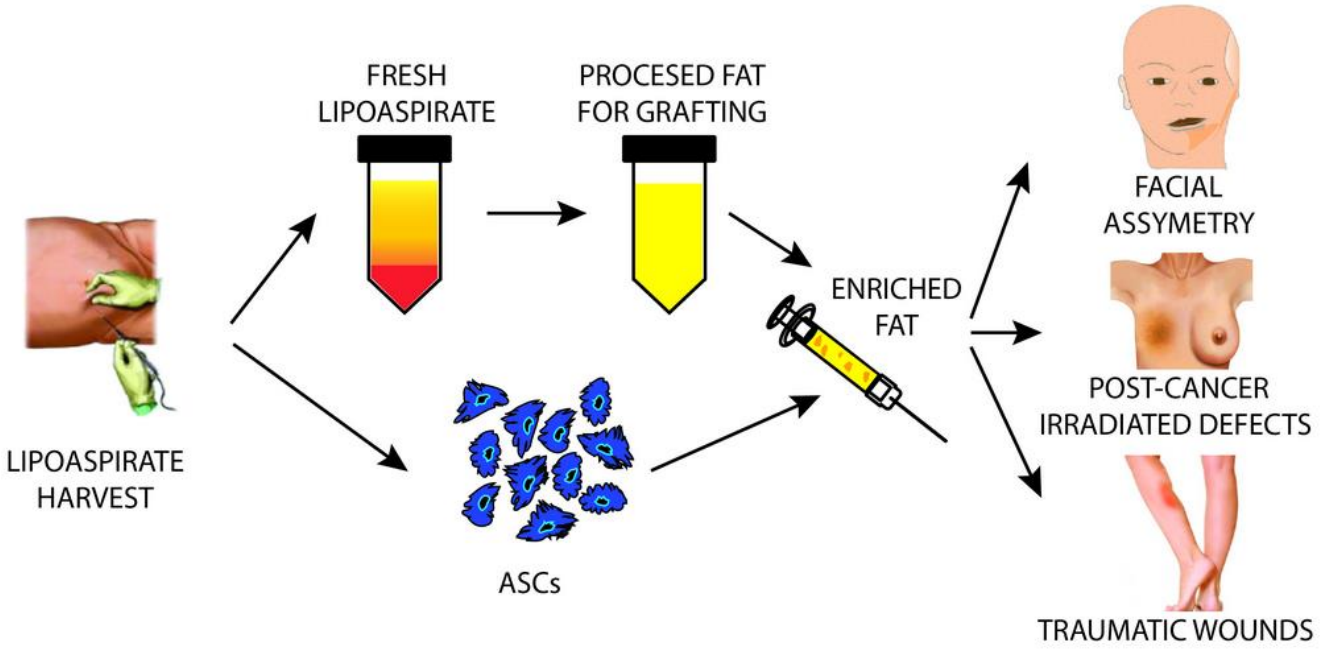
  - Minimally invasive
  - Autologous rejuvenation method
  - Less complications
  - Long-lasting effects

Cell Assisted Lipotransfer

Autologous fat transfer, is a common technique used for soft tissue reconstruction from 100 years ago, however, resorption rate is 50% to 80% after 1 year

To improve the fat graft survival rate, cell-assisted lipotransfer (CAL) have been introduced

In this technique, fat is enriched with stromal vascular fraction (SVF) obtained after enzymatic digestion of fat



Royan Skin Clinic Experience

We enrolled 10 patients with mean age of 46.2 years (36- 58)

Safety:

- No major complication
- 1 ecchymosis, 5 local edema, 3 pains that dissolved in 1 month

Efficacy (1 year follow up): Mean survival rate: 56.25% (20- 90%)




Autoimmune diseases

Brain
Multiple Sclerosis
Guillaun-Barre Syndrome
Autism

Thyroid
Thyroiditis
Hashimoto's Disease
Graves' Disease

Blood
Leukemia
Lupus Erythematosus
Hemolytic Dysglycemia

Bones
Rheumatoid Arthritis
Ankylosing Spondylitis
Polymyalgia Rheumatica

GI Tract
Celiac's Disease
Crohn's Disease
Ulceratic Colitis
Diabetes Type I

>100 Autoimmune Diseases

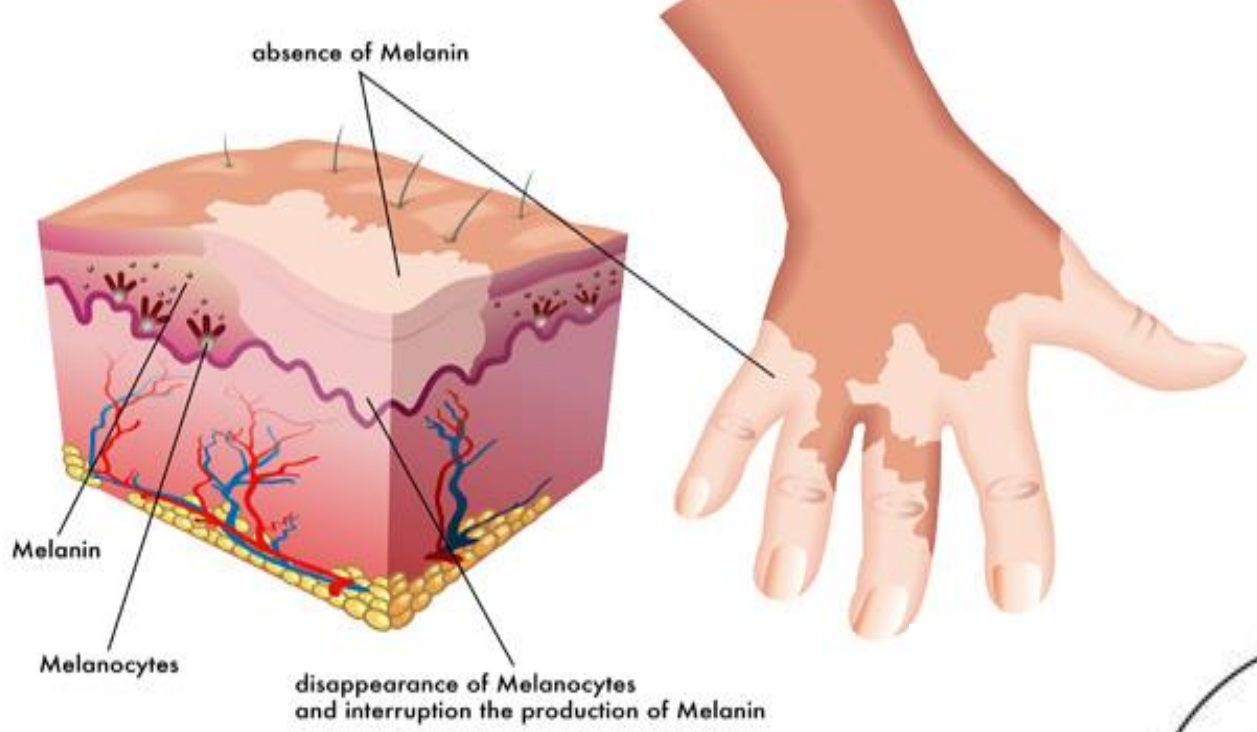
Muscles
Muscular Dystrophy
Fibromyalgia

Nerves
Peripheral Neuropathy
Diabetic Neuropathy

Skin
Psoriasis
Vitiligo
Eczema
Scleroderma

Lung
Fibromyalgia
Wegener's Granulomatosis

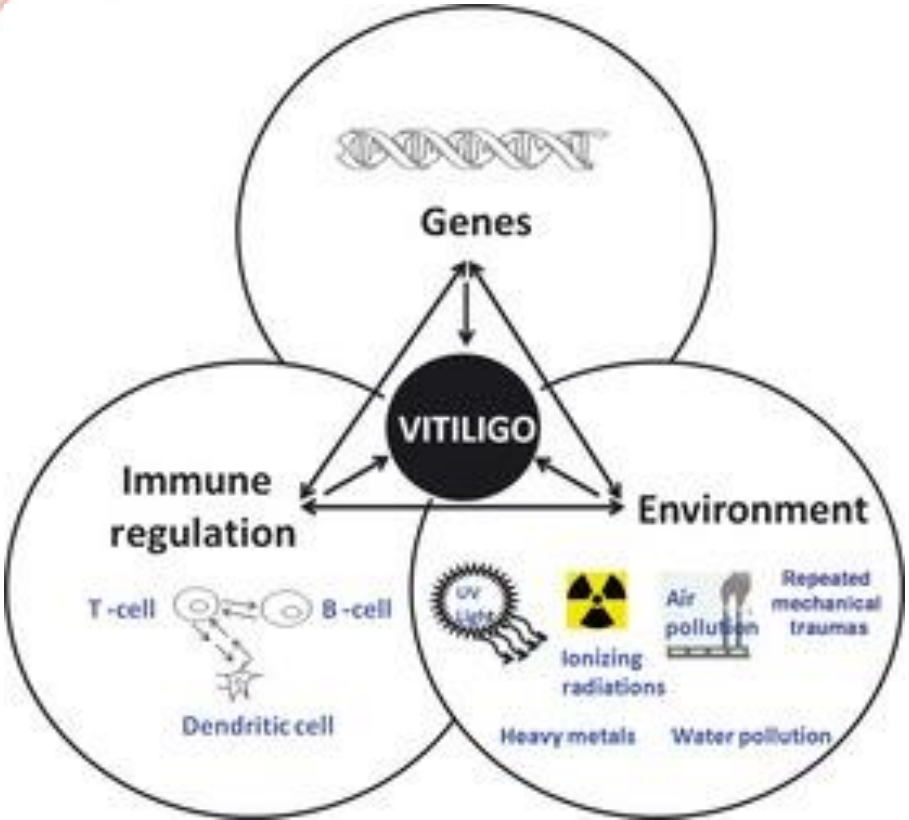
Vitiligo



0.5-2% of worldwide population

Pathogenesis:

- Self destruction
- Neurtoxicity
- Autoimmune



Royan Skin Clinic Experience

Autologous Non- cultured Melanocyte Transplantation

Enrollment

Assessed for eligibility

Excluded
- Disease activity
- Age <12 years old
- Previous treatments

allocated to receive autologous epidermal cell suspension

Intervention

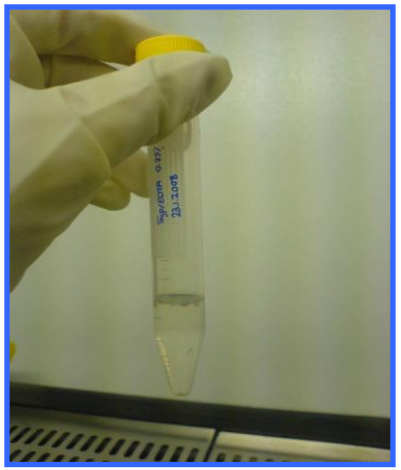
Partial thickness sampling of gluteal skin (1/3-1/7 of recipient area)

Epidermal cell suspension preparation

Intra-epidermal injection of cell suspension (0.05-0.1 ml/cm^2)

Outcome Evaluations

Follow up



Arch Dermatol Res
DOI 10.1007/s00403-010-1034-7

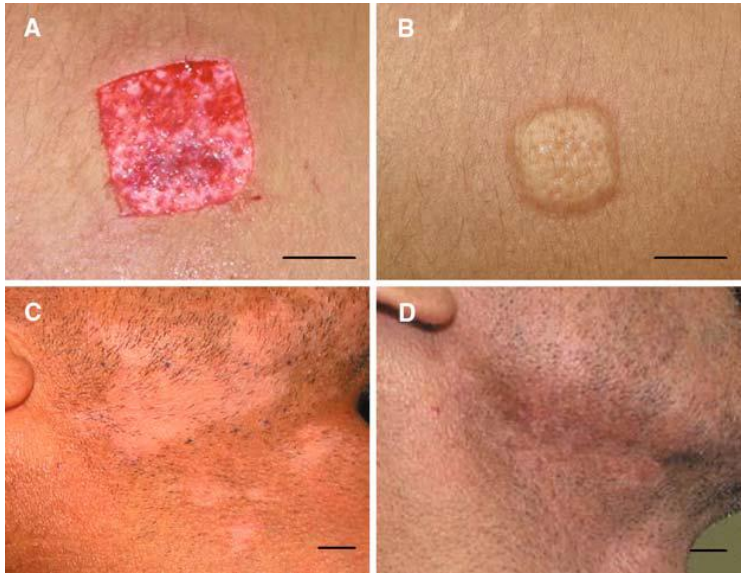
ORIGINAL PAPER

Intraepidermal injection of dissociated epidermal cell suspension improves vitiligo

Laleh Khodadadi · Saeed Shafieyan · Masoud Sotoudeh · Ahmad Vosough Dizaj · Abdolhossein Shahverdi · Nasser Aghdami · Hossein Baharvand

Received: 13 November 2009 / Revised: 21 January 2010 / Accepted: 25 January 2010
© Springer-Verlag 2010

- 10 vitiligo patients



Repigmentation (6 m)	Percent of patients
>75%	40%
51-75%	20%
26-50%	20%
<25%	20%

Contents lists available at ScienceDirect

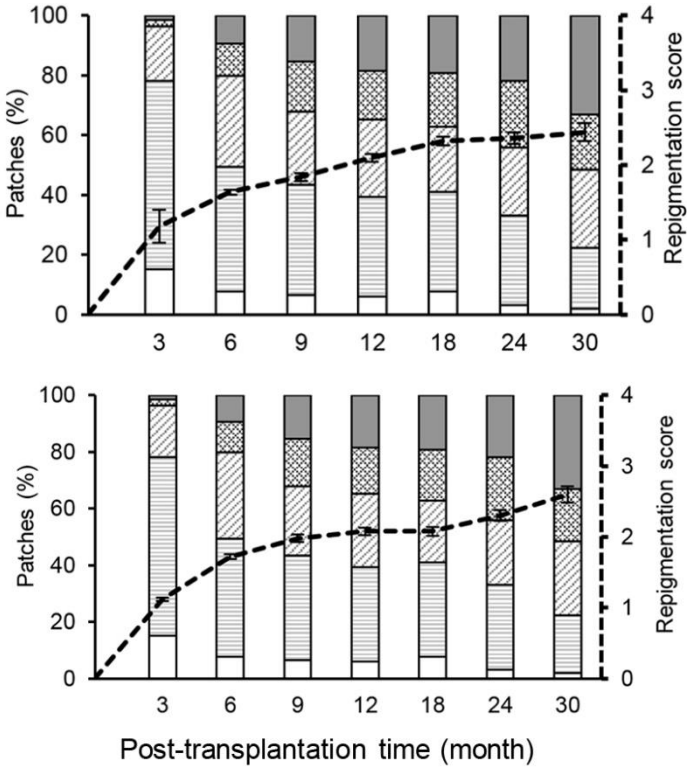
Journal of Dermatological Science

journal homepage: www.elsevier.com

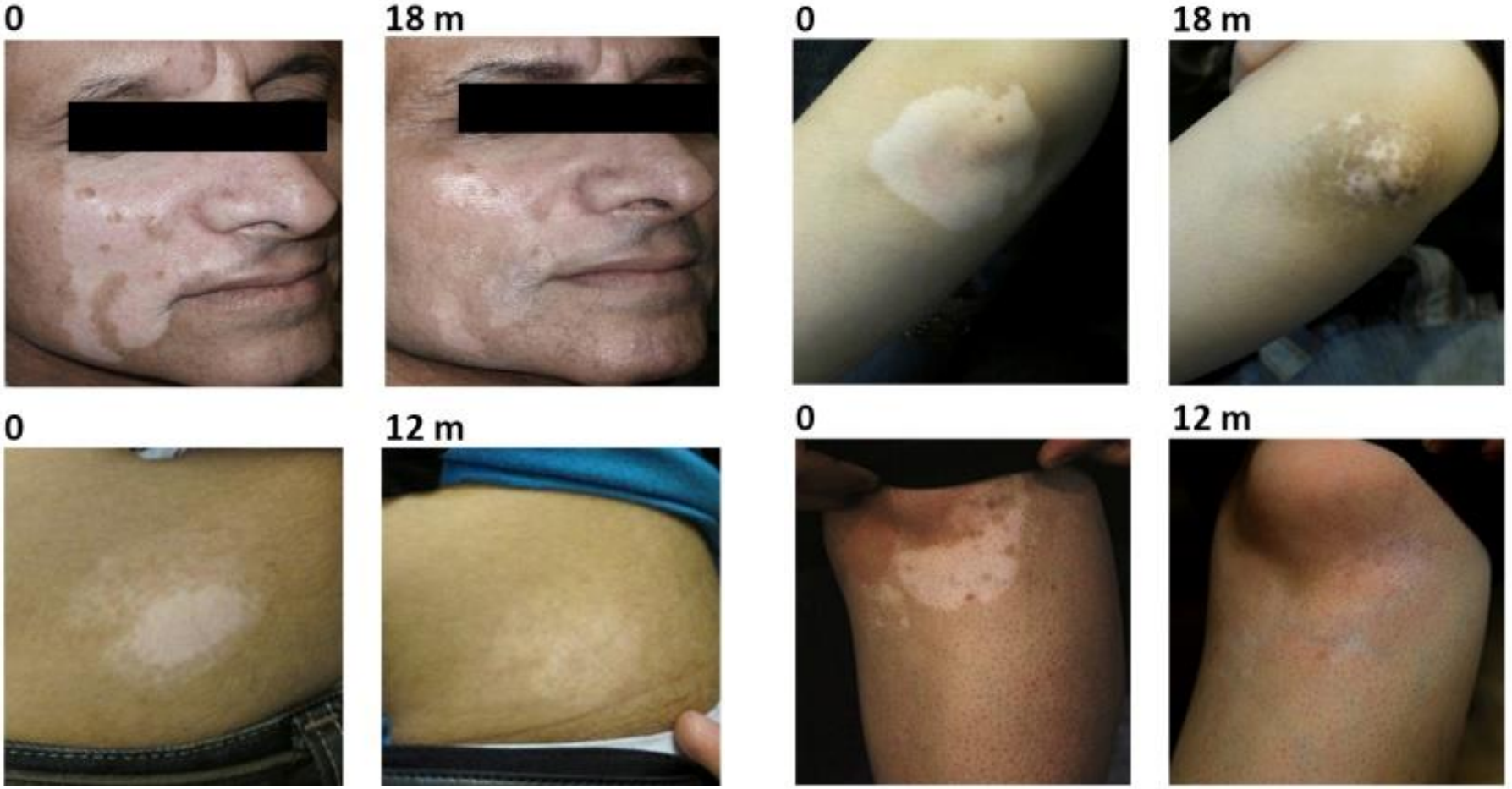
A single-arm open-label clinical trial of autologous epidermal cell transplantation for stable vitiligo: A 30-month follow-up

Zahra Orouji[a, 1], Amir Bajouri[a, 1], Mahshid Ghasemi[a, 1], Parvaneh Mohammadi[a], Nasrin Fallah[a], Atefeh Shahbazi[a], Mohammad Rezvani[a], Fatemeh Vaezirad[a], Zahra Khalajasadi[a], Ahad Alizadeh[b], Ehsan Taghiabadi[a], Sara Dashtbozorgi[a], Raheleh Aghdami[a], Seyedeh Esmat Hosseini[a], Hossein Bahahrvand[a], Saeed Shafieyan[a, *], Nasser Aghdami[a, *]

[a] Department of Regenerative Medicine, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran
[b] Department of Epidemiology and Reproductive Health, Reproductive Epidemiology Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran



- The largest trial on cell therapy in vitiligo (1060 patches in 300 patients)
- Intralesional injection is safer, more tolerable, and less expensive than current techniques
- Effective in stable vitiligo, especially for patches on face and neck
- repigmentation stability in 79.3% of patches


0
18 m
0
18 m
0
12 m
0
12 m

Burns and Wounds

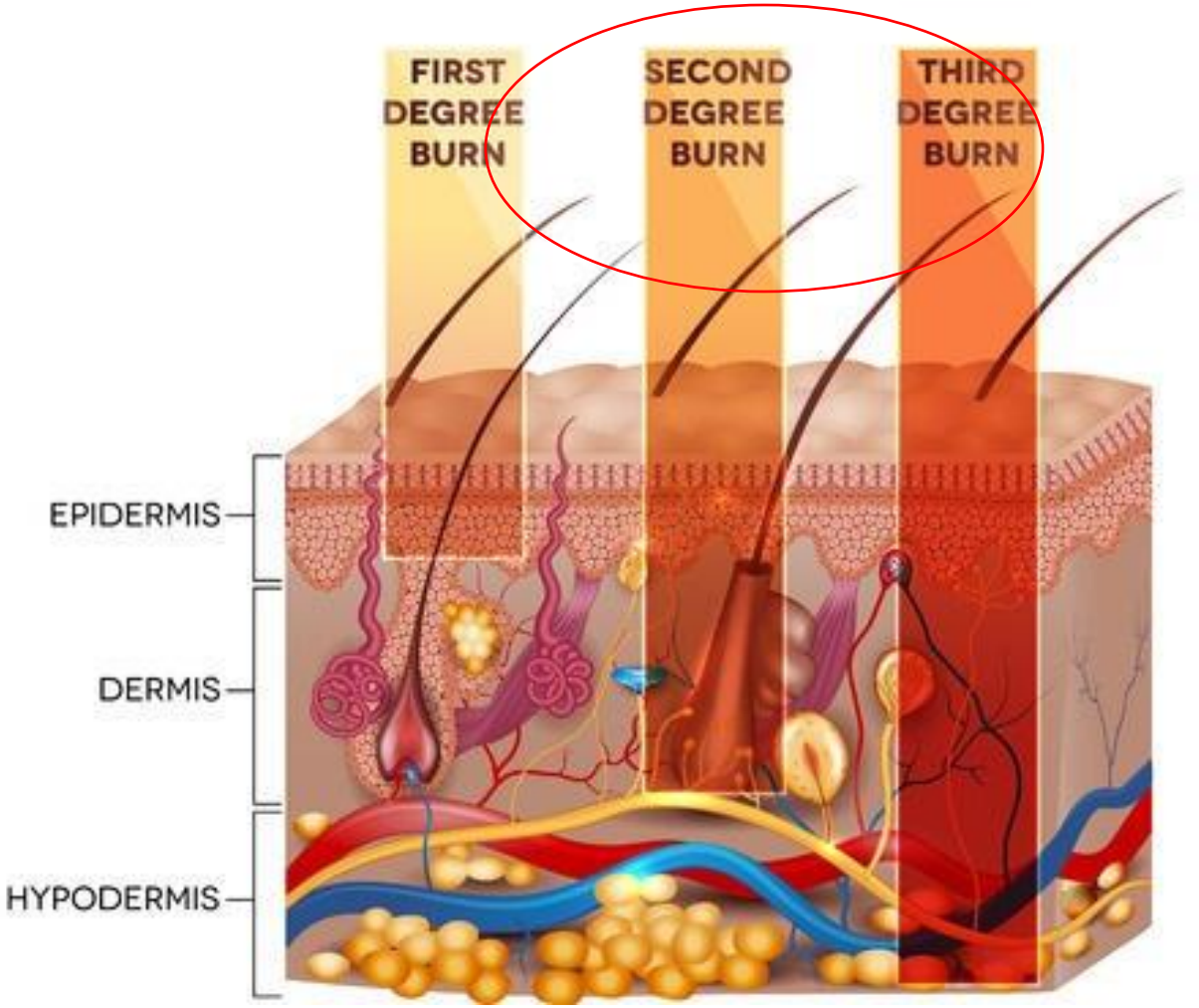
Burns

- 1.1 per 100.000
- Highest rate in southeast Asia
- 250,000 deaths every year
- 32%– 72% leads to scar

Diabetic foot ulcer

- 15% of diabetic patients
- 5% progress to amputation
- 84% of lower-leg amputations

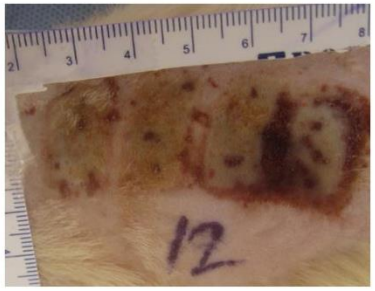
Burn wounds

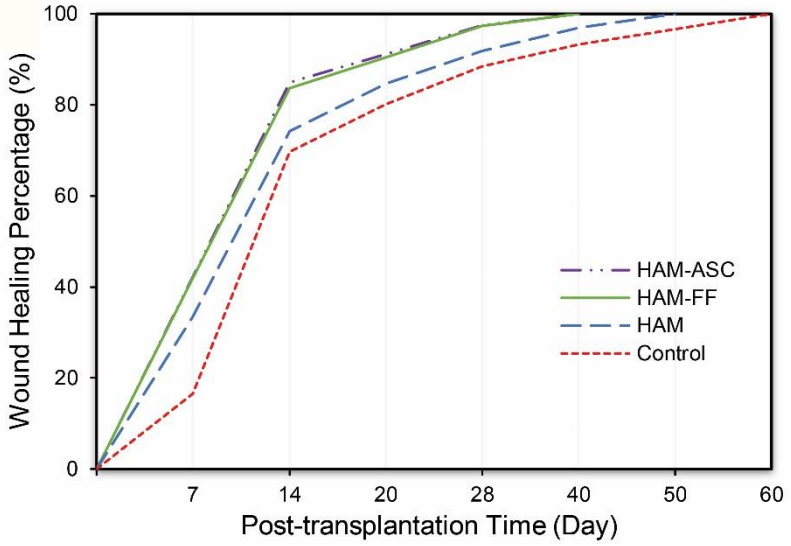

FIRST DEGREE BURN
SECOND DEGREE BURN
THIRD DEGREE BURN
EPIDERMIS
DERMIS
HYPODERMIS

Royan Skin Clinic Experience; Pre-clinical

Third degree burns of 1100-1800 mm^2 were induced on 32 Sprague-Dawley rats.

Burned sites were excised and randomly covered with Vaseline gauze (control), human amniotic membrane (HAM), human fetal fibroblasts seeded on HAM (HAM-FF), or human adipose-derived stem cells seeded on HAM (HAM-ASC)

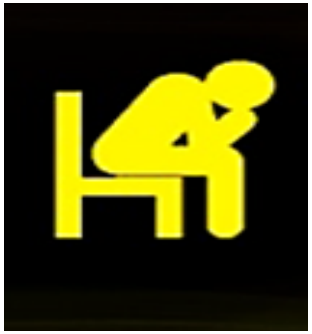




Post-burn hypertrophic scar (HTS)

Red firm raised Inflexible tissue
following 32%– 72% of burns

Complications

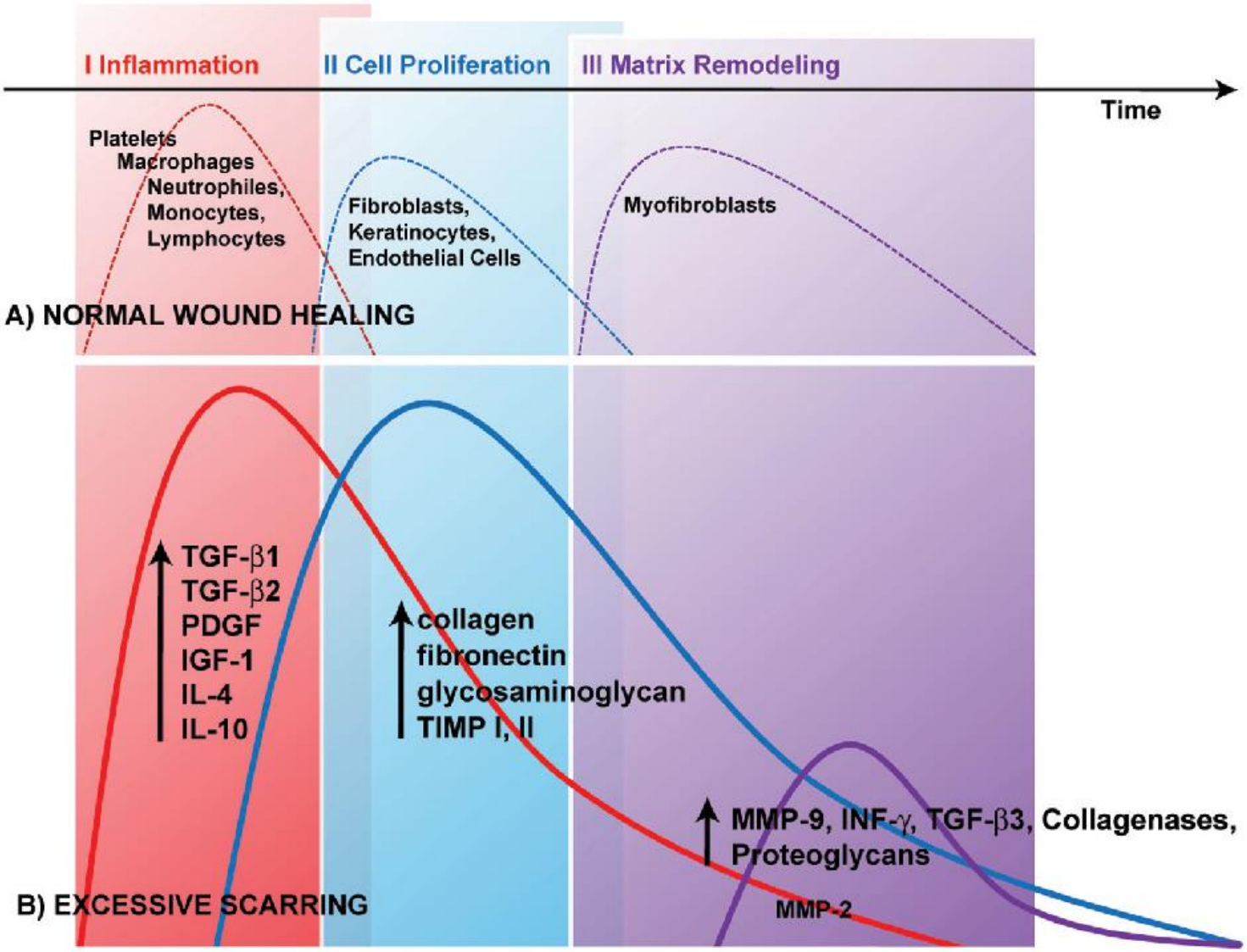


Psychologic

Functional

Gauglitz et. al, Mol Med 2011

HTS Pathogenesis



Gauglitz et. al, Mol Med 2011

Anti-scar potential of Mesenchymal Stem Cells

Zhang *et al. Stem Cell Research & Therapy* (2015) 6:145
DOI 10.1186/s13287-015-0133-y

stem cell research&therapy

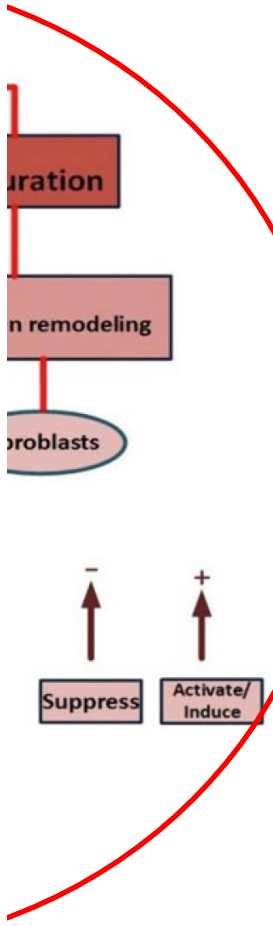
RESEARCH Open Access

Intralesional injection of adipose-derived stem cells reduces hypertrophic scarring in a rabbit ear model

Qi Zhang[1†], Li-Na Liu[1†], Qi Yong[2], Jing-Cheng Deng[1] and Wei-Gang Cao[1*]

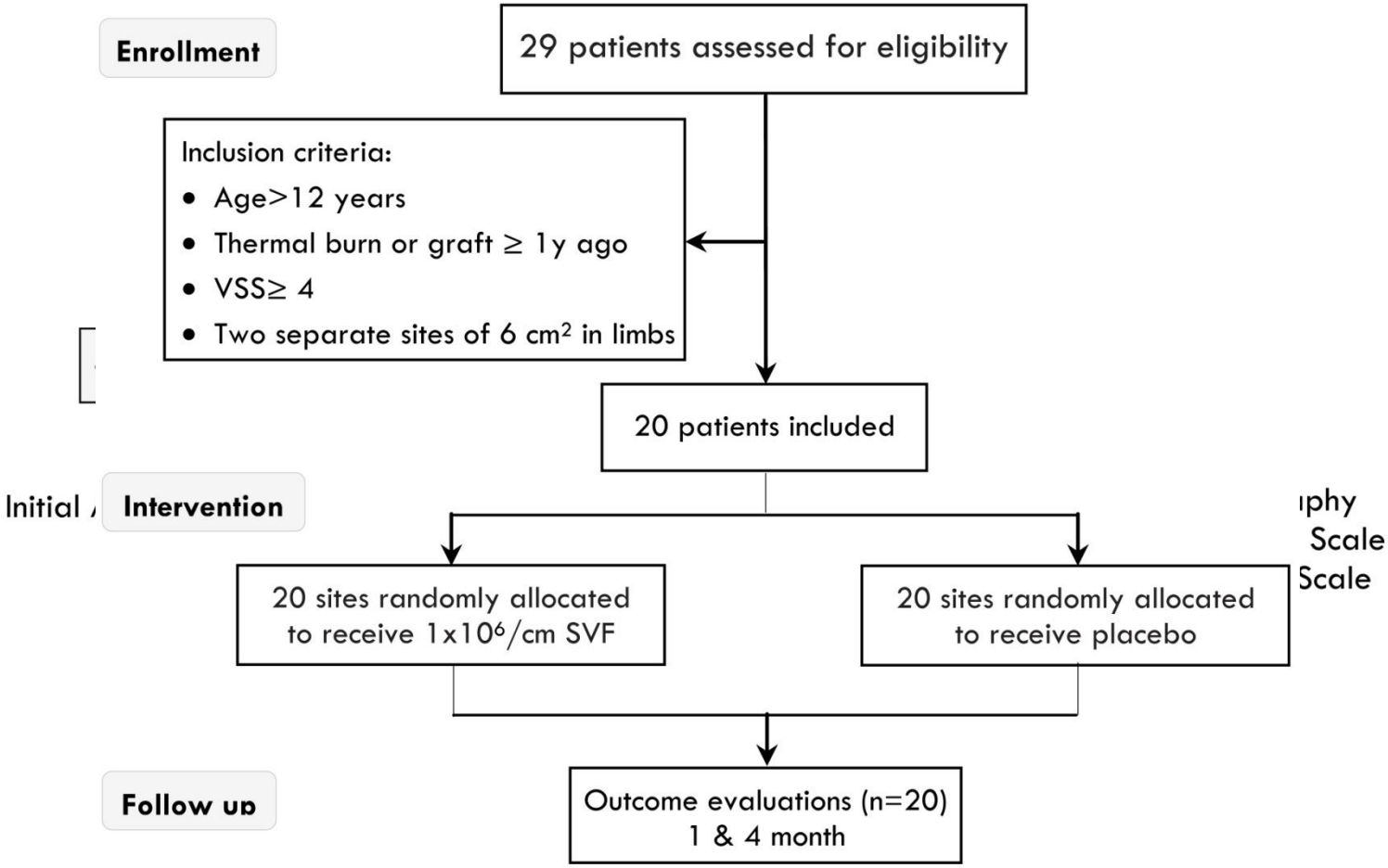
An intralesional injection of ASCs reduces the formation of rabbit ear hypertrophic scars by decreasing the α-SMA and collagen type I gene expression and ameliorating collagen deposition and this may result in an effective and innovative anti-scarring therapy.

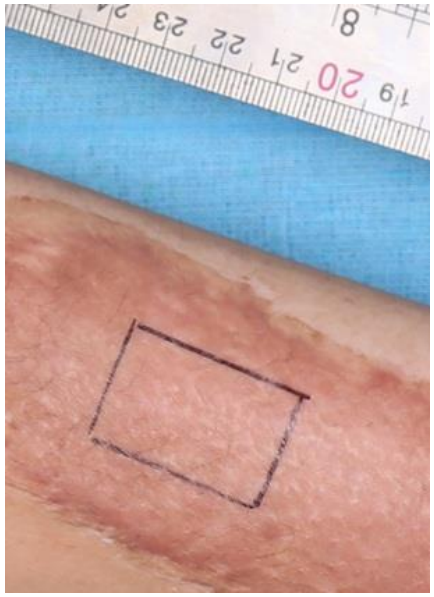
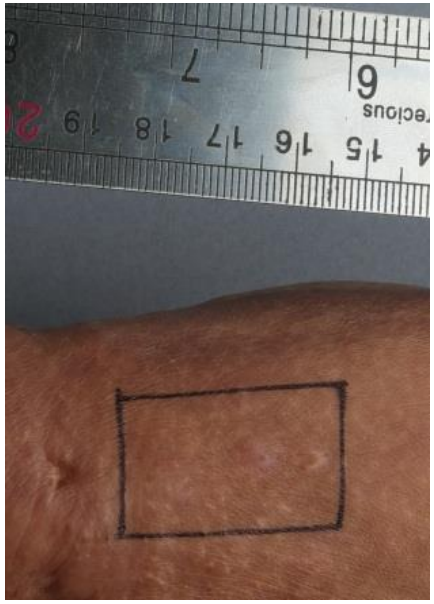
Conclusions: An intralesional injection of ADSCs reduces the formation of rabbit ear hypertrophic scars by decreasing the α-SMA and collagen type I gene expression and ameliorating collagen deposition and this may result in an effective and innovative anti-scarring therapy.



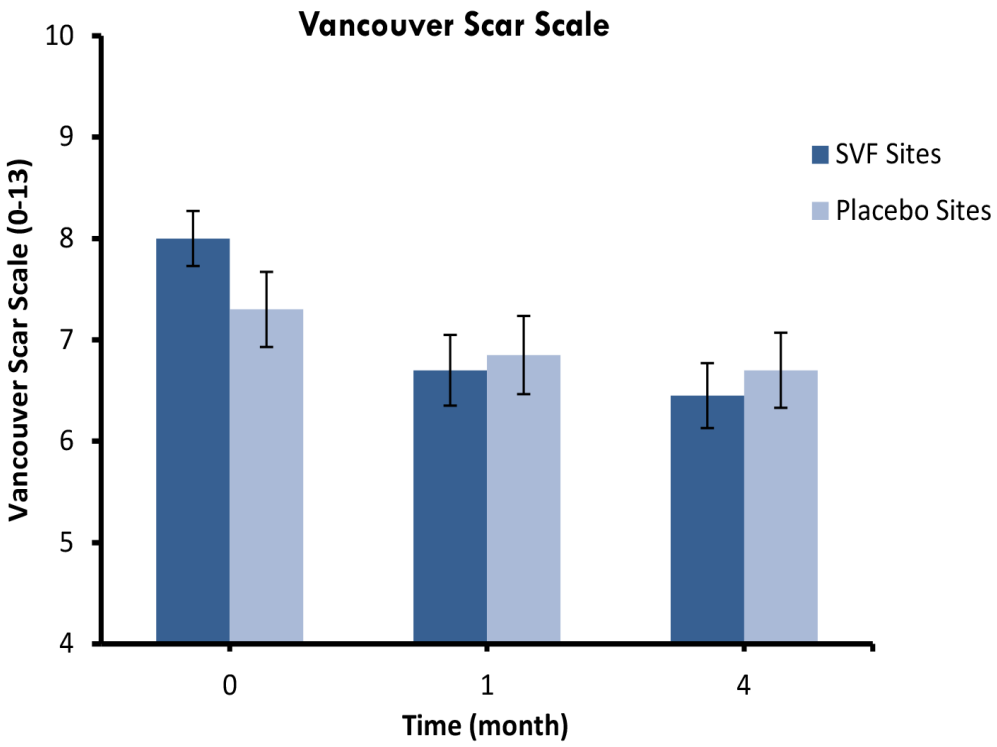
Jackson et al. Stem Cells Transl Med 2012, Goodarzi et al. Adv Exp Med Biol 2018

Study Design

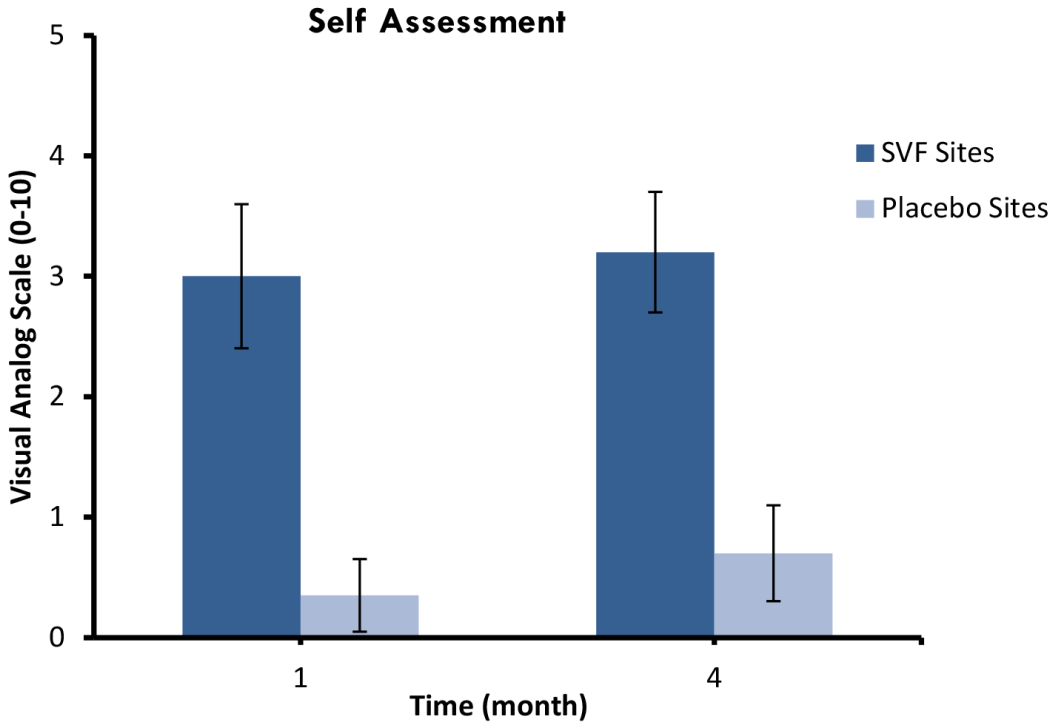


	Before	After
Control		
Case		

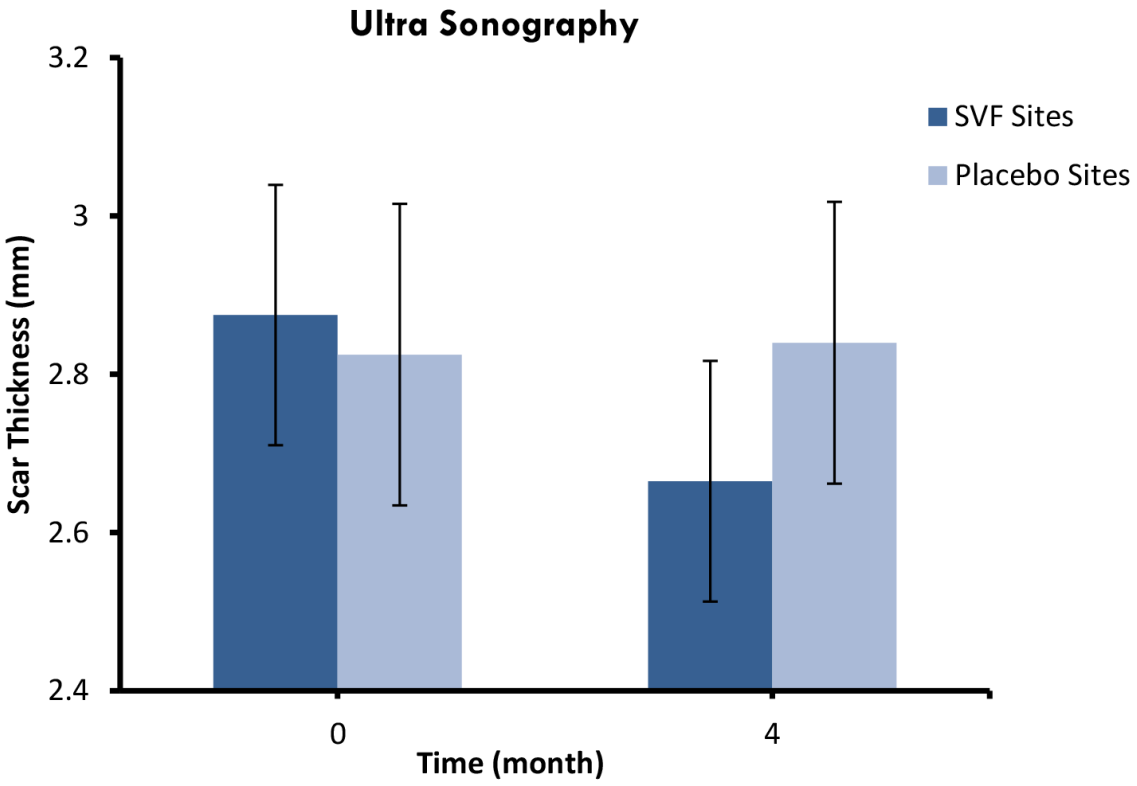
Efficacy Outcome: VSS



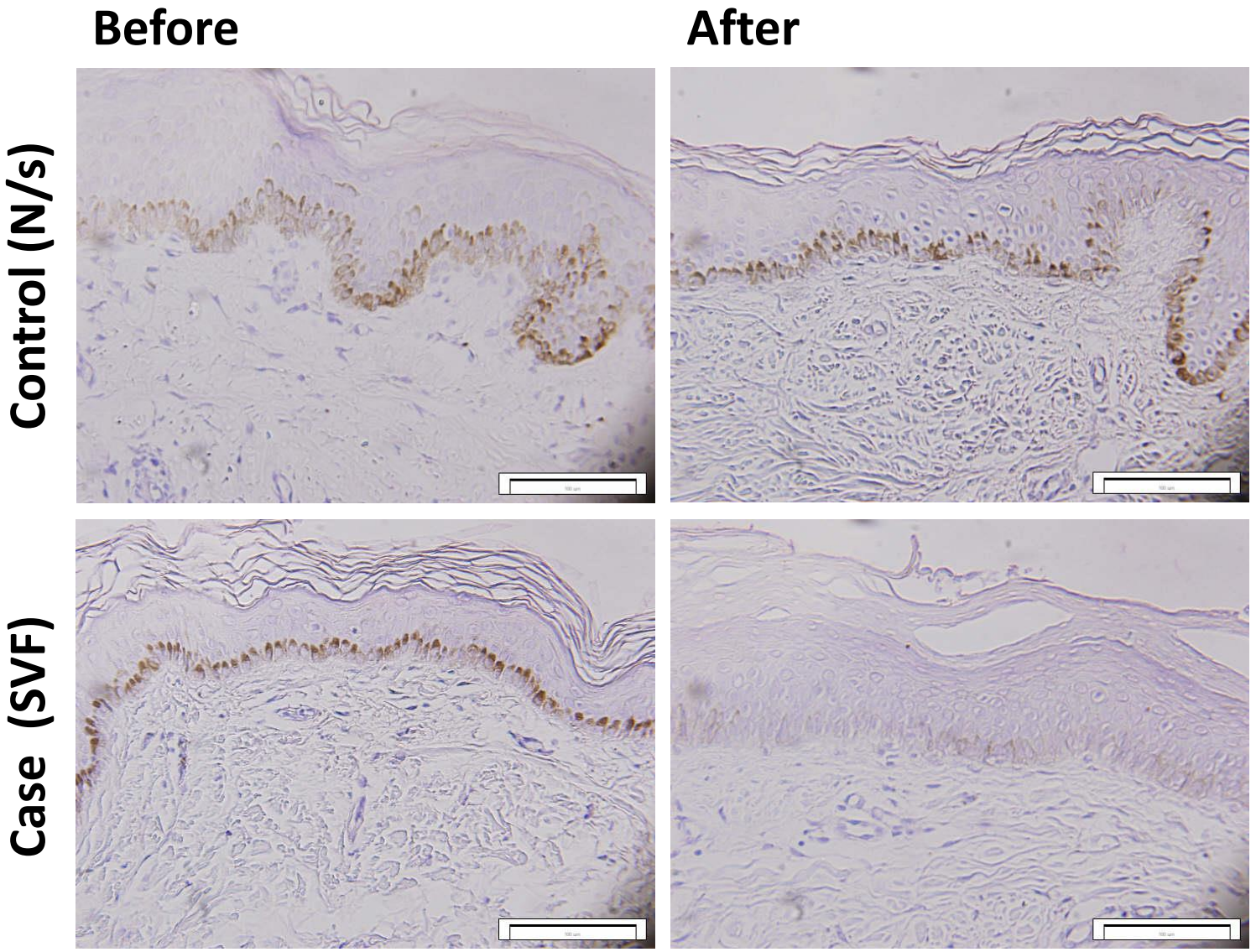
Efficacy Outcome:
Patients self assessment (VAS)



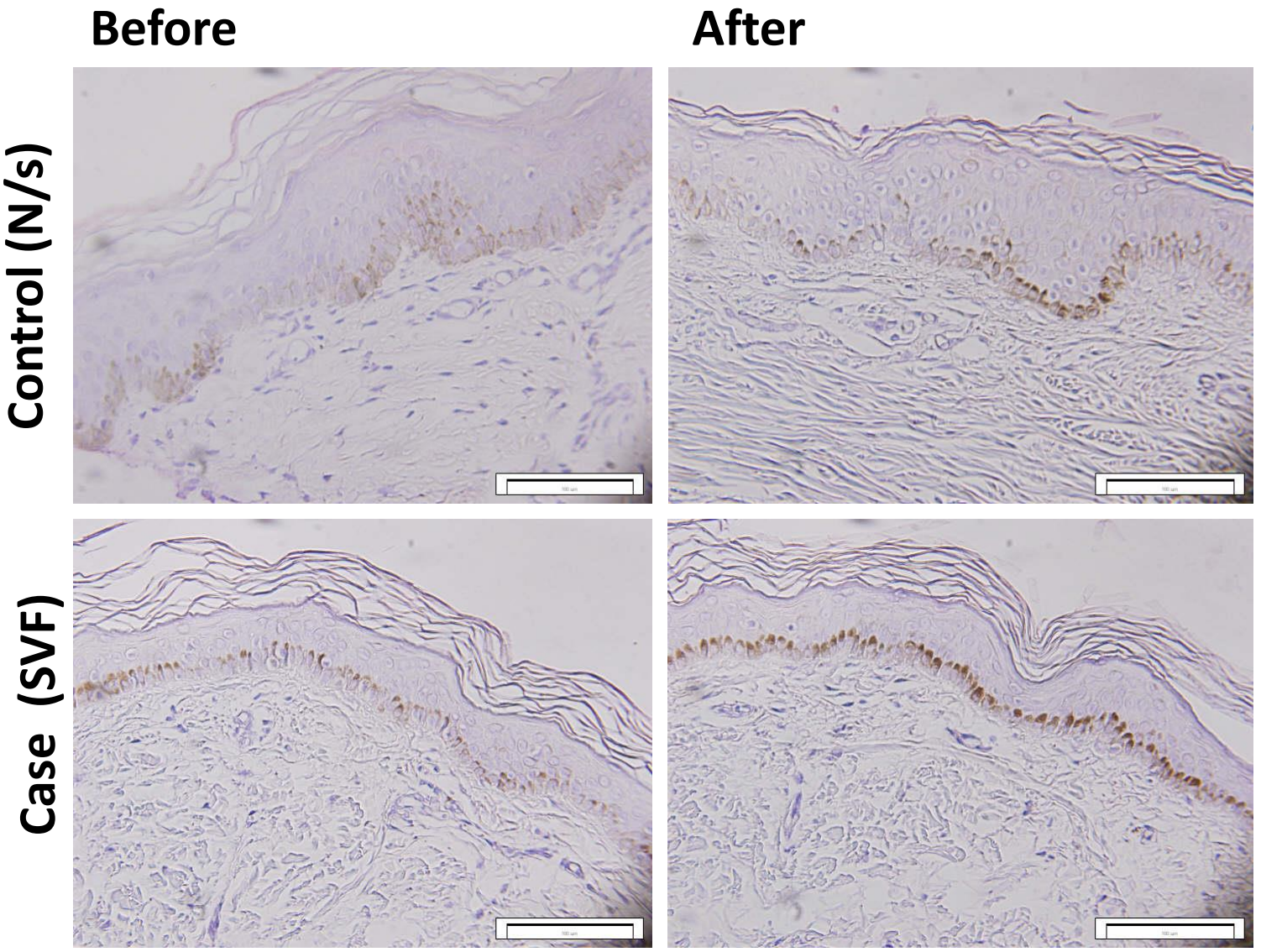
Efficacy Outcomes: Ultrasound Imaging



Underlying mechanism: IHC results (TGF-B1)



Underlying mechanism: IHC results (TGF-B3)



Epidermolysis Bullosa

"The Worst Disease You've Ever Heard Of"

Introduction

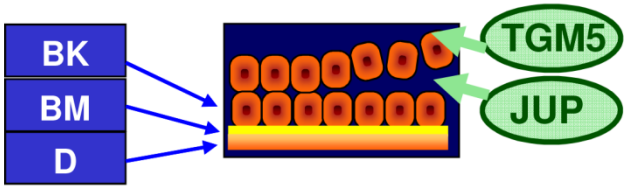
- A group of inherited connective tissue diseases (16 genes)
- First described by Von Hebra in 1870
- Prevalence: 2-4 per 100.000
- Average life expectancy: 30 years

Appearance:

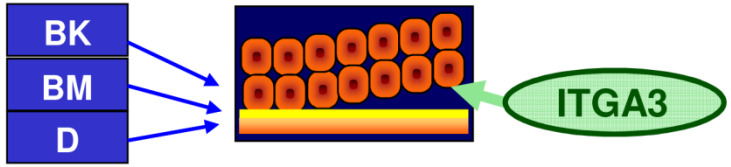
- Blister formation, in response to minor injury, heat, or friction
- Blisters may occur inside the body, such as intestines, in severe cases

Types

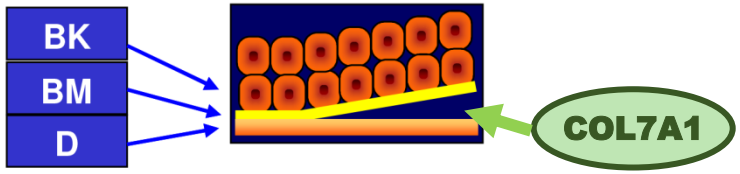
Intraepidermal: EB simplex (EBS)

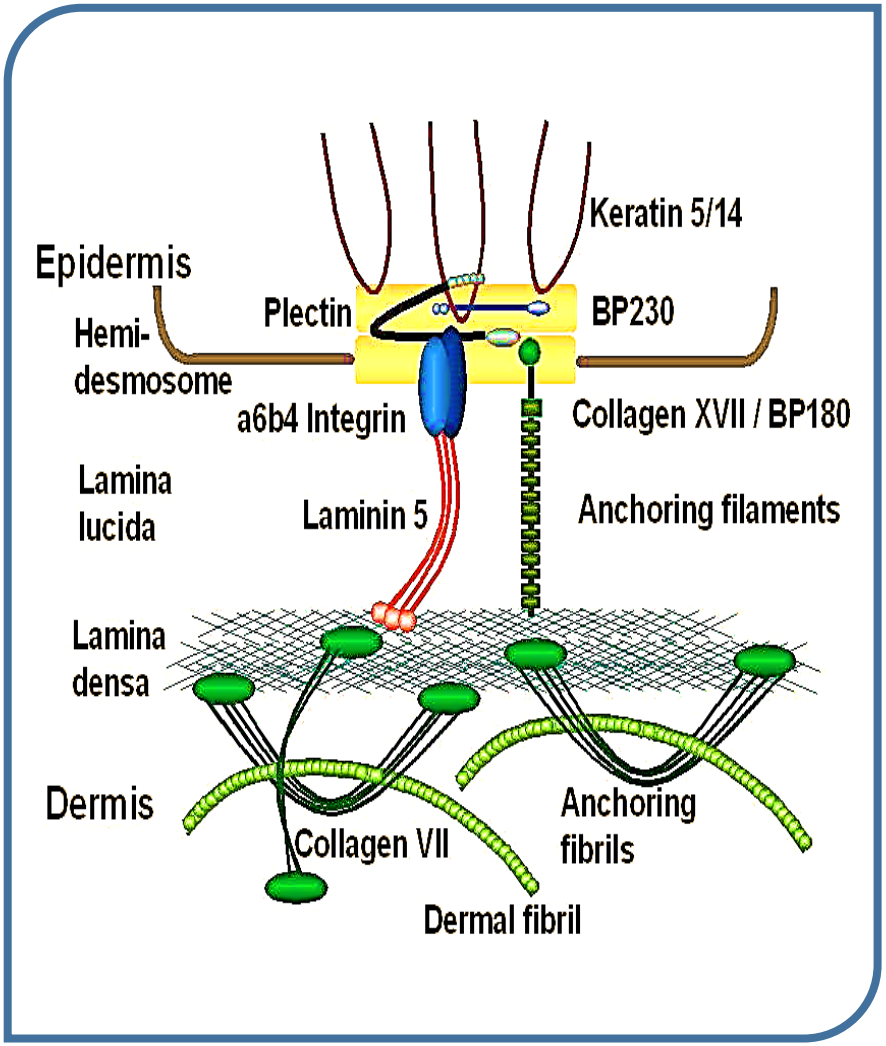


Intra-lamina lucida: junctional EB (JEB)



Sub-lamina densa: dystrophic EB (DEB)





Treatments

- Introduced from 2005
- Locally graft the allogenic fibroblasts, keratinocytes or MSC

Limitations:

- Need for re-transplantation

Regenerative medicine

- **Protein therapy**
- **Gene therapy**
- **Cell therapy**

Royan Skin Clinic Experience

Eligibility criteria:
Age 2-30
DEB with mitten hand
No severe anemia
No immune deficiency

Initial assessment

Skin biopsy

Hand surgery

Histopathology
Manual muscle test (MMT)
Healing evaluation

Follow up visits

Cell culture

Amniotic Membrane

Autologous Fib + AM

Allogenic Fib + AM

1 m | 3 m | 6 m | 9 m | 12 m


سوختگی
اولین همایش بین المللی
سوختگی

Amniotic Membrane

Autologous Fib + AM

Allogenic Fib + AM

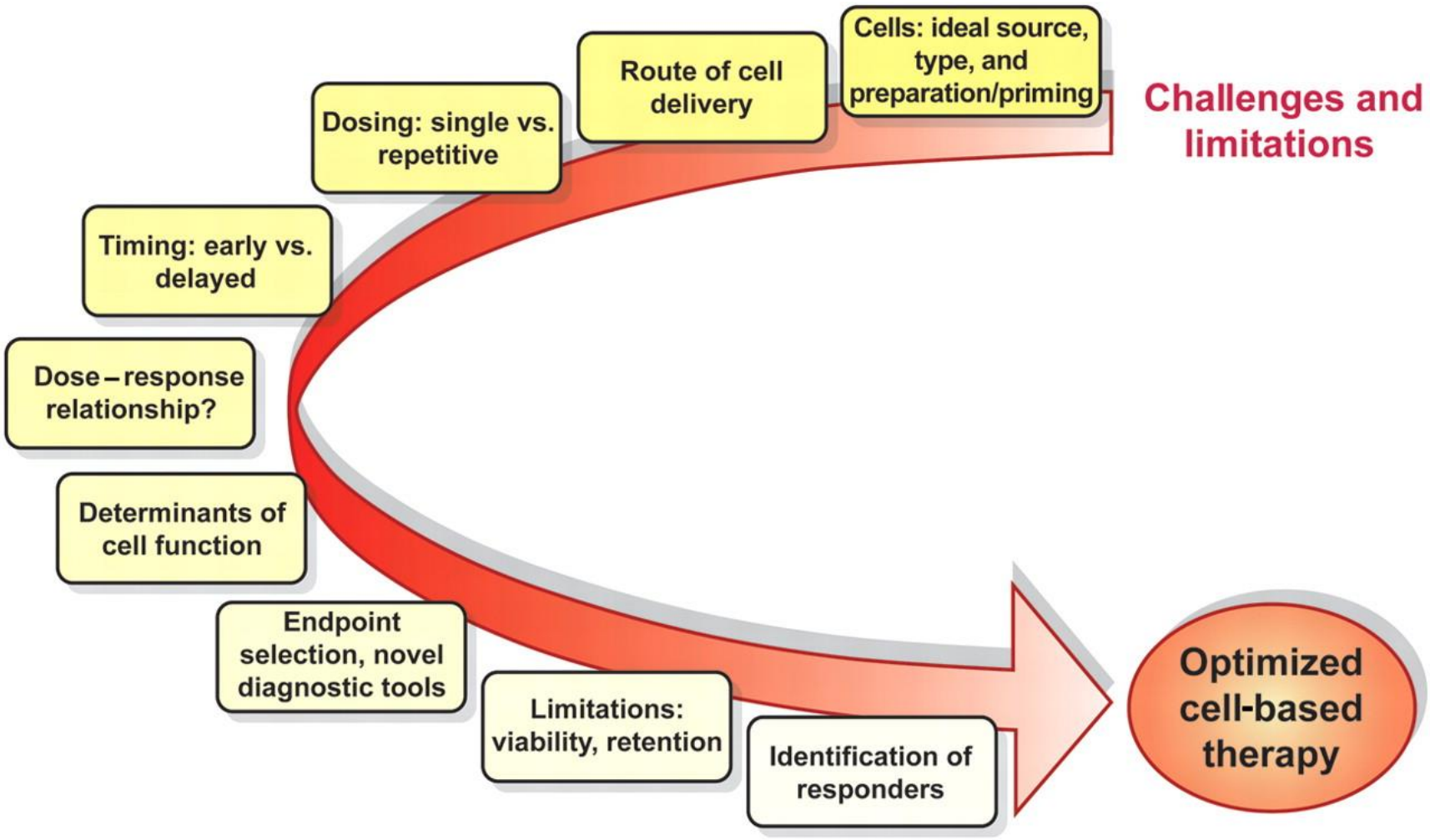
Before 2 months 6 months

Patients

- 15 patients were included, underwent the surgery and followed for 12 months
- Mean age: 8.8 ± 8.6
- 10 male (66.6%)
- All patient's parents had familial marriage
- 5 patients (33.3%) had previous hand surgery
- 5 patients (33.3%) had previous esophageal surgery

Conclusion

- Allogenic fibroblasts transplantation could be a promising modality for DEB
- Need for re-transplantation
- Approach to gene therapy


Cells: ideal source, type, and preparation/priming
Route of cell delivery
Dosing: single vs. repetitive
Timing: early vs. delayed
Dose–response relationship?
Determinants of cell function
Endpoint selection, novel diagnostic tools
Limitations: viability, retention
Identification of responders
Challenges and limitations
Optimized cell-based therapy

THANK YOU

FOR YOUR ATTENTION