ELEVENTH WORLD CONFERENCE ON
THE FUTURE OF SCIENCE™

Precision Medicine:
present challenges for future cures

VENICE, SEPTEMBER 17-19 2015

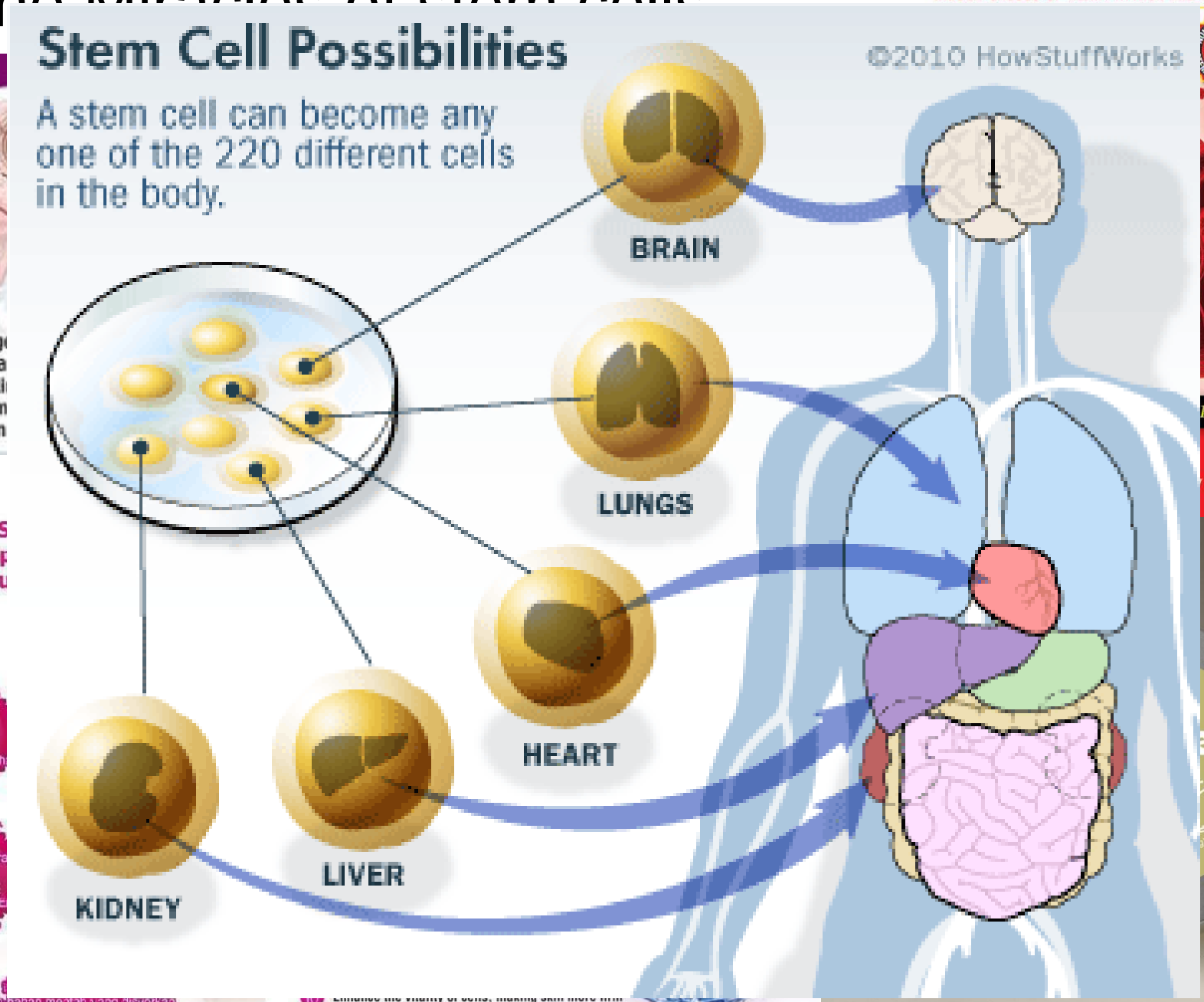
REGENERATIVE MEDICINE TODAY: ACHIEVEMENTS, HOPES AND HYPE

Giulio Cossu

Institute of Inflammation & Repair
University of Manchester

Department of Biosciences
University of Milan

The Miracles of stem cells



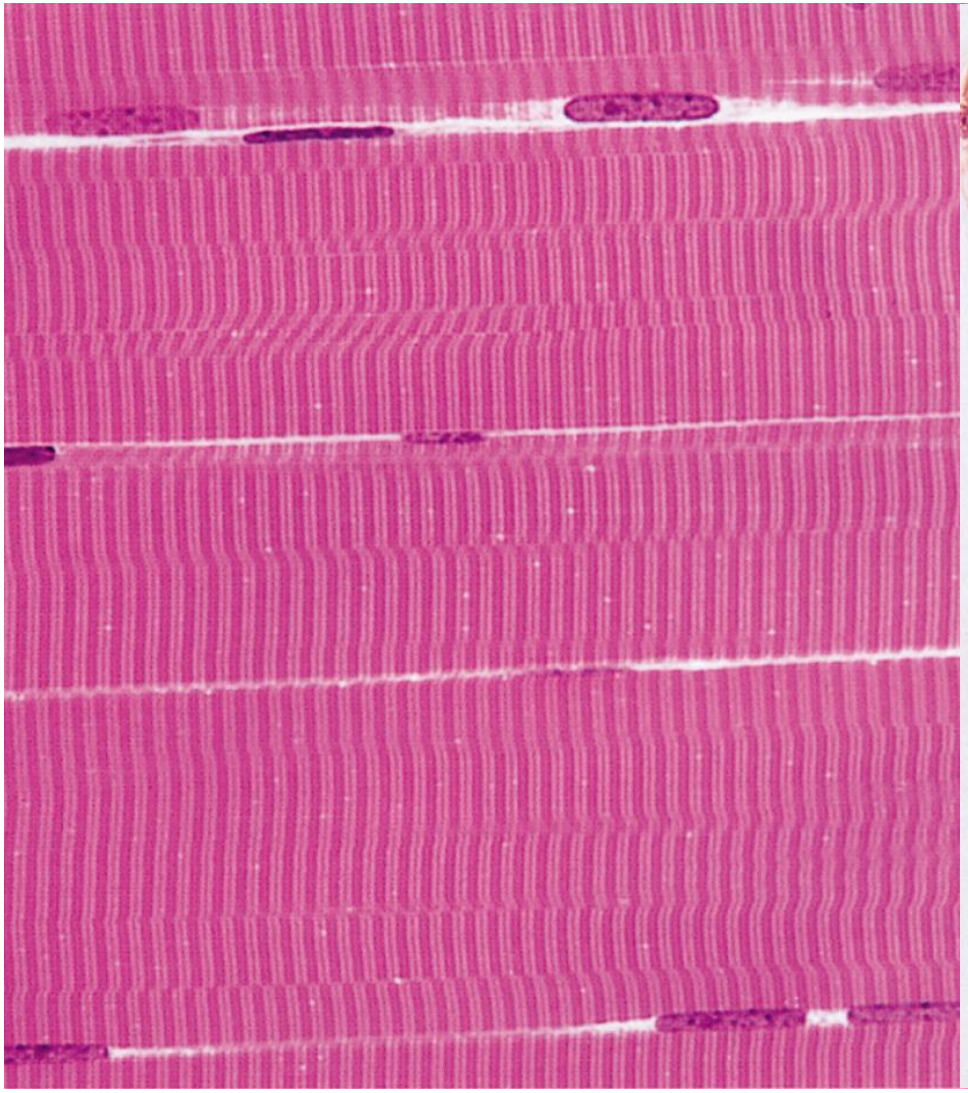
Giulio Bizzozzero: Labile, stable and permanent cells

- Giulio Bizzozzero (1846-1901, Professor of Pathology at the University of Turin) found that erythropoiesis/leukopoiesis takes place in bone marrow [1868]; he discoverd platelets. Furthermore, Bizzozzero understood that cell renewal varied in different tissues and classified them as:

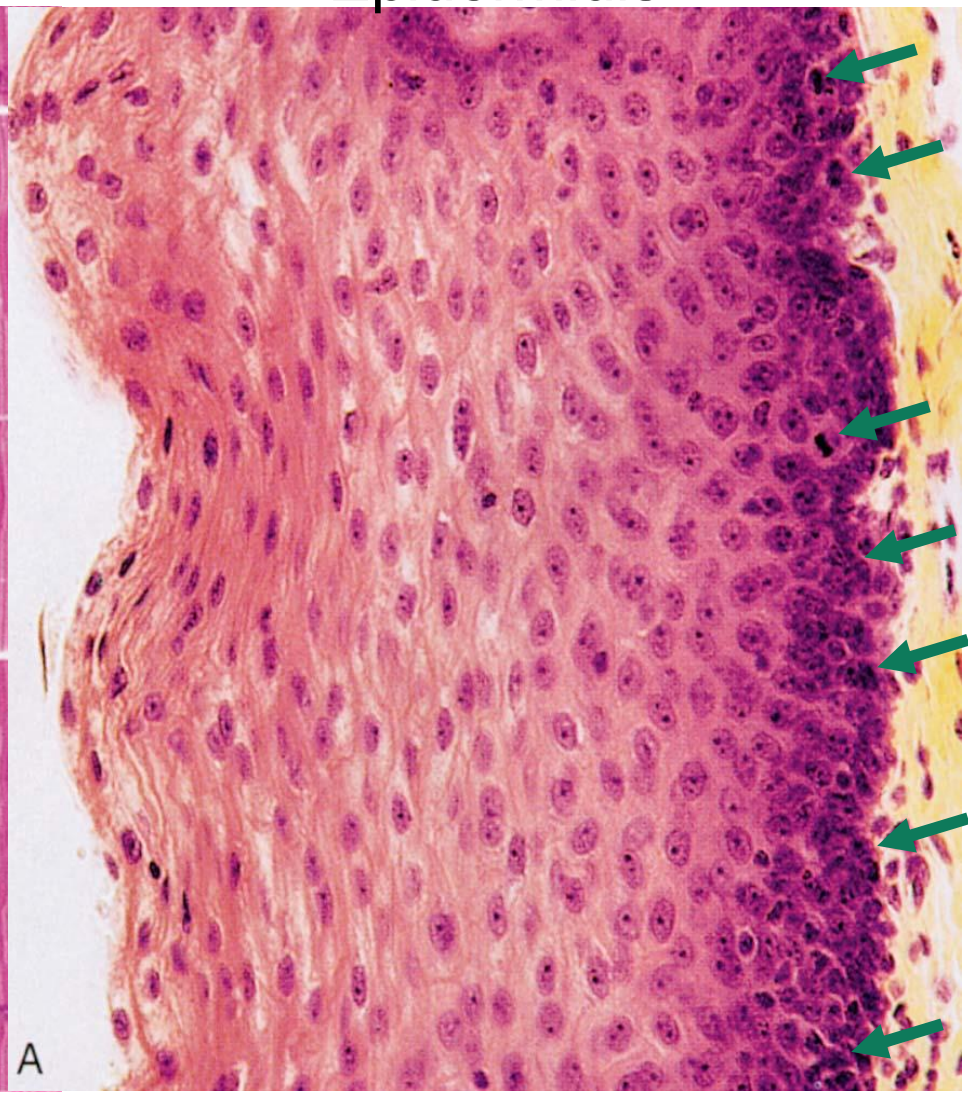
- labile (e.g. bone marrow)
- stable (e.g. liver)
- permanent (e.g. nervous)

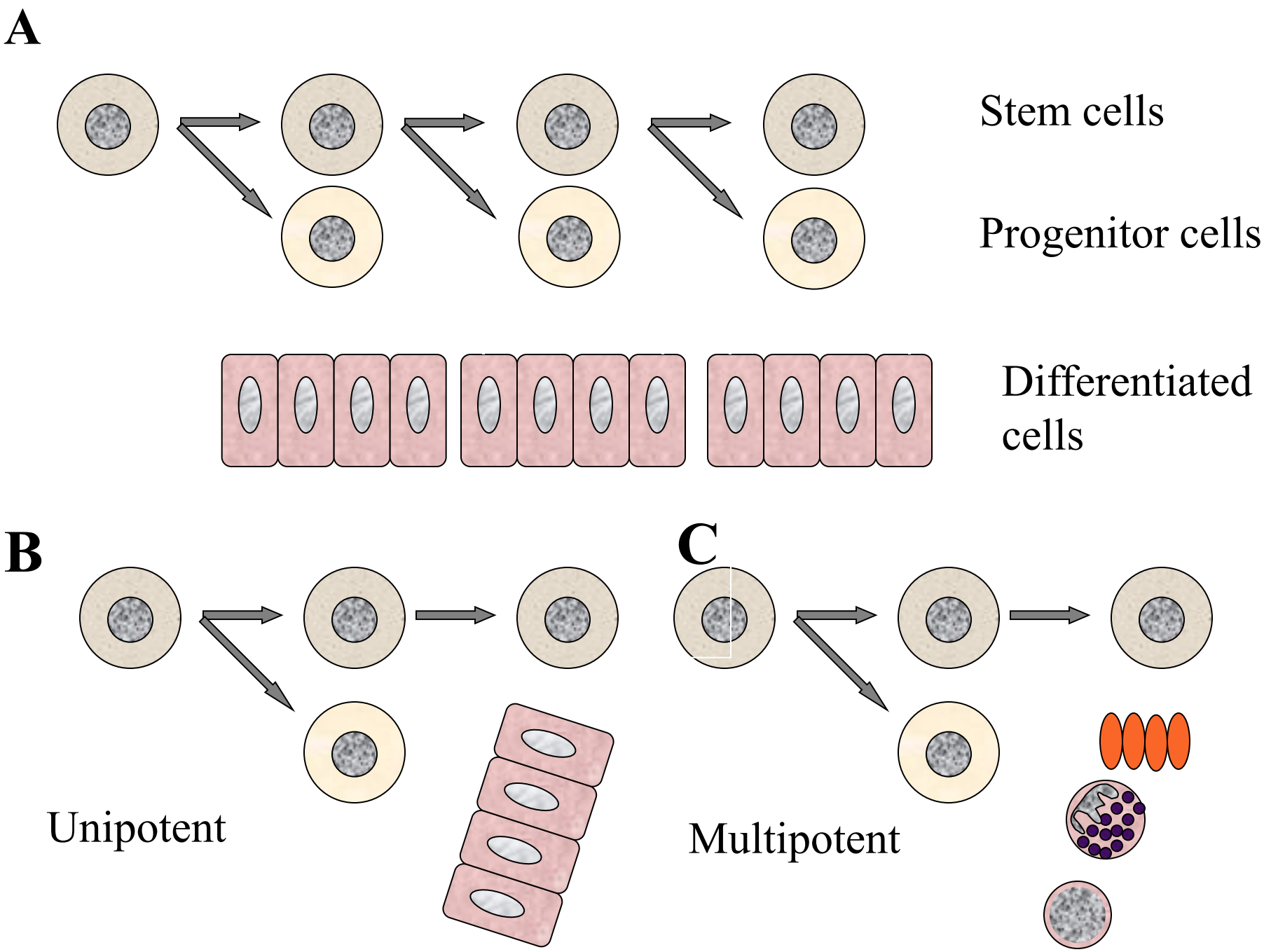
Skeletal and cardiac muscle or brain contain very few mitotic cells while epithelia and bone marrow have many

Skeletal muscle

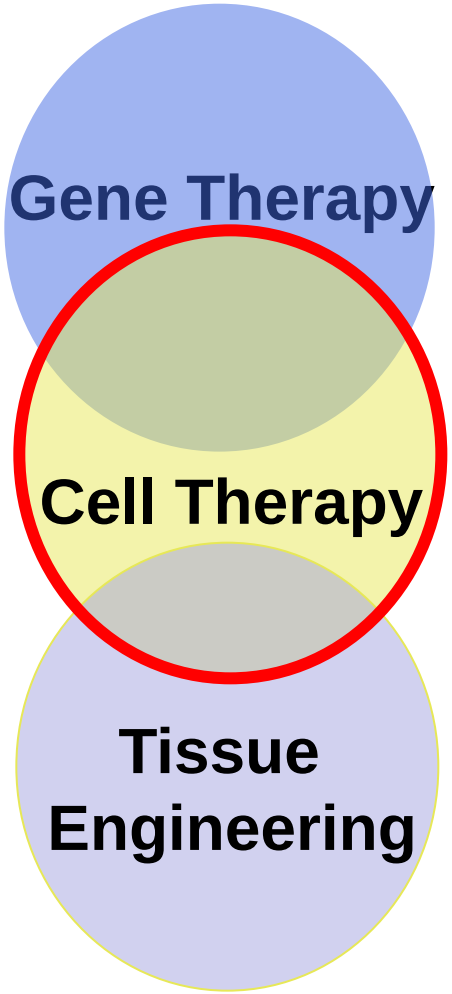


Epidermidis




A
Stem cells
Progenitor cells
Differentiated cells
B
Unipotent
C
Multipotent

Regenerative medicine:



The drug is a gene (cDNA) carried by a modified virus (vector) or other molecules

The drug is a cell, in some case corrected in culture by a viral vector

The drug is a tissue (or whole organ) composed by biomaterials and cells

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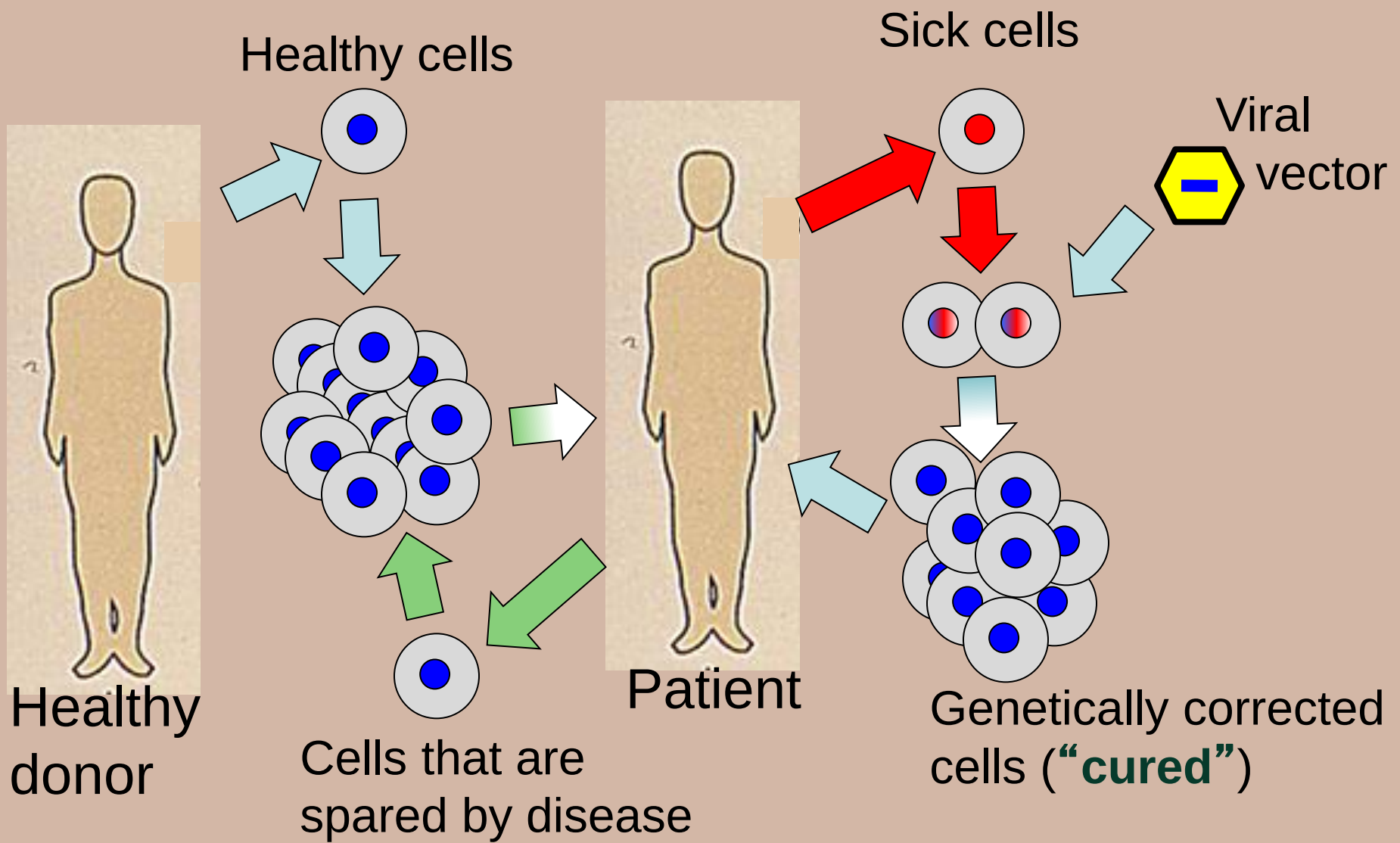
Cell Therapy

Personalized medicine: **YES**

Precision medicine: **NOT REALLY**

Cell therapy: two main strategies

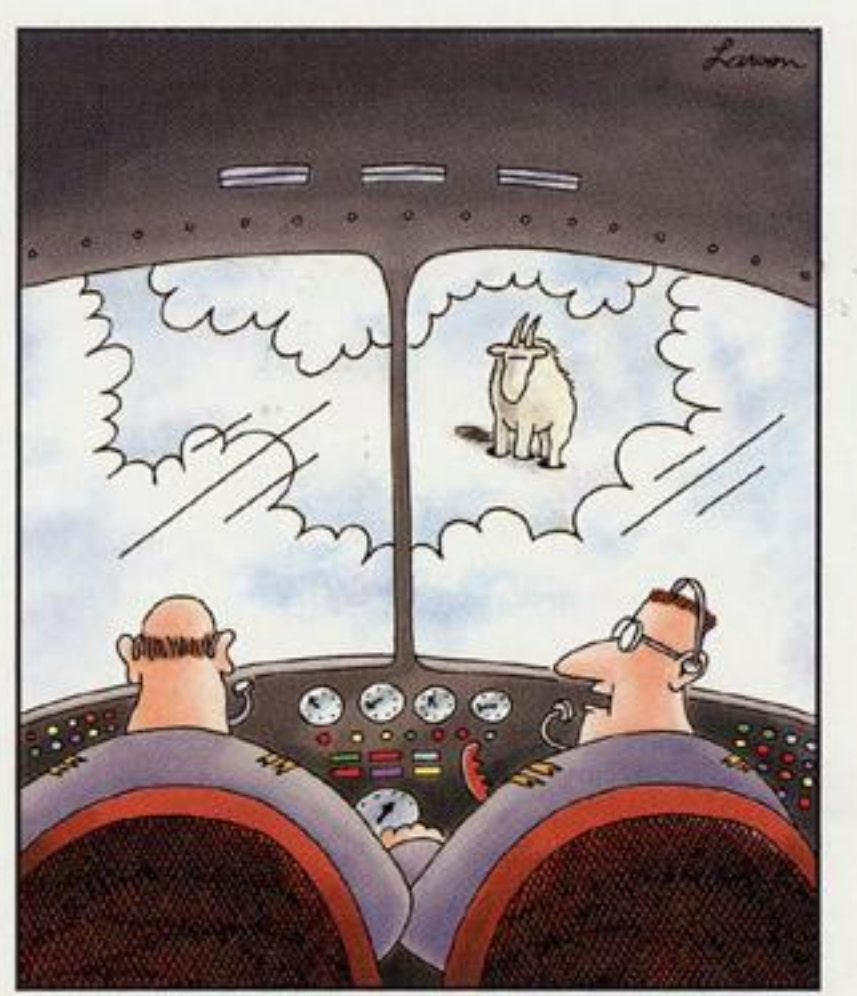


Cell therapy: not without risks

Serious diseases:

- No existing, efficacious therapy
- Careful analysis of risks/benefit ratio
- Careful analysis of possible future impact

The possible risk



Say… what's a mountain goat doing way up here in a cloud bank?

What are the parameters that stem cells must satisfy to predict efficacy in pre-clinical and clinical trials?

1. They must be present in the donor tissue in sufficient number (or may be propagated in vitro)
2. They must be able to reach the target tissue in high numbers, survive, eventually compete with resident cells (but do not proliferate indefinitely and eventually form a tumor).
3. They should produce efficiently the needed differentiated progeny and functionally integrate in the host tissue.
4. Most importantly……

Which diseases are cured today with stem cells ?

In clinical practice :

1. Bone marrow transplantation for hematological diseases
2. Auto-transplantation of epidermis for large burns
3. Corneal unilateral burns
4. Congenital immune deficiencies

In clinical experimentation:

1. Epidermolysis bullosa
2. Severe lesions of the skeleton
3. Parkinson disease
4. Muscular dystrophy and many others

Bone marrow transplantation of patient's hematopoietic stem cells, after ADA transfer led to a permanent cure (15 years for the first patient)

No PEG-ADA

Busulfan
2 mg/Kg/day x 2
(days -3, -2)

Day -4: Purification of BM CD34⁺ cells

Day 0: Infusion

ADA **Neo**

MLV LTR

Days -3 to -1:
3 cycles of transduction on retronectin + cytokines

Day-4: Prestimulation (TPO, FLT3-ligand, SCF, IL-3)

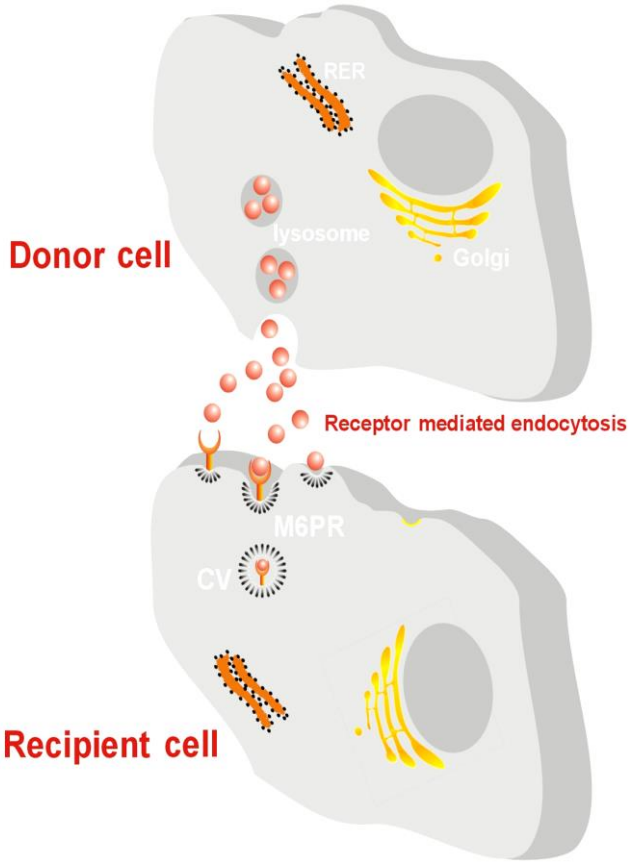
Aiuti et al. Science, 2002

Treatment of Lysosomal Storage Disease based on cross-correction

- Cells lack an enzyme to digest their metabolic products
- These accumulate, engulf and kill cells, mainly neurones
- Low levels of enzyme are sufficient to reduce/abolish symptoms
- Therapeutic implications:

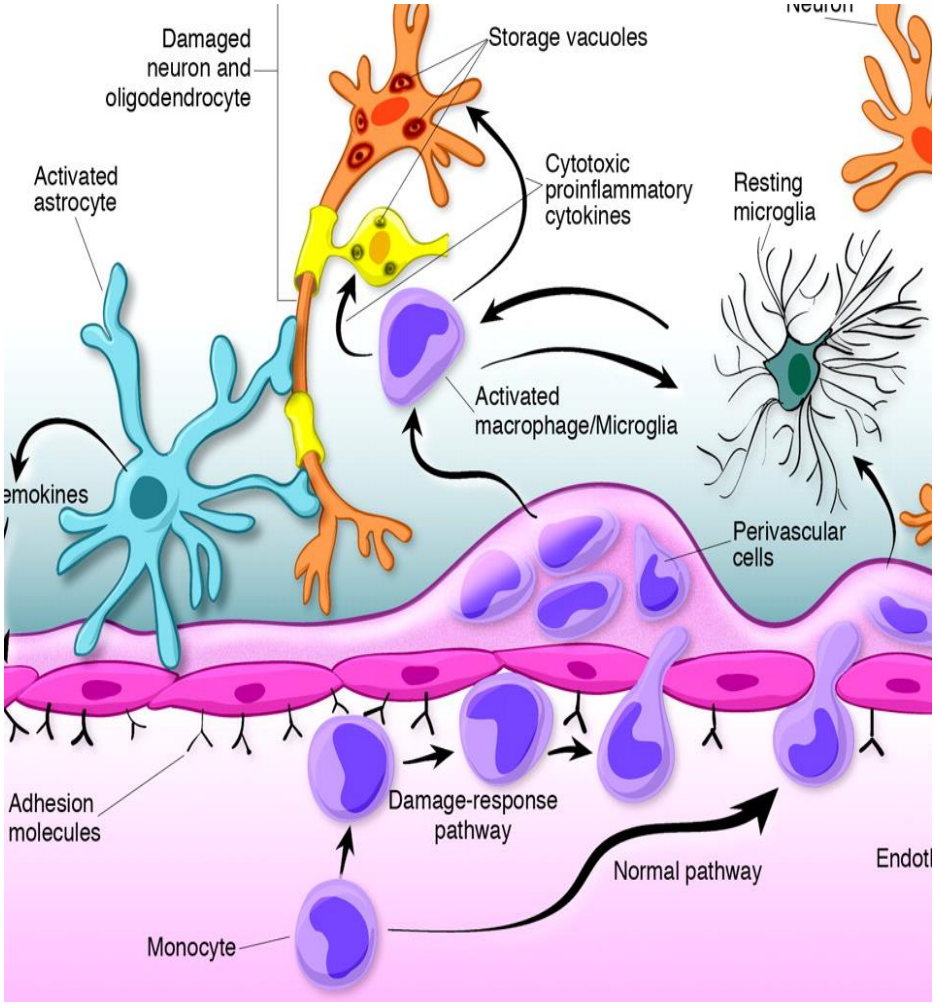
a) Enzyme replacement strategies

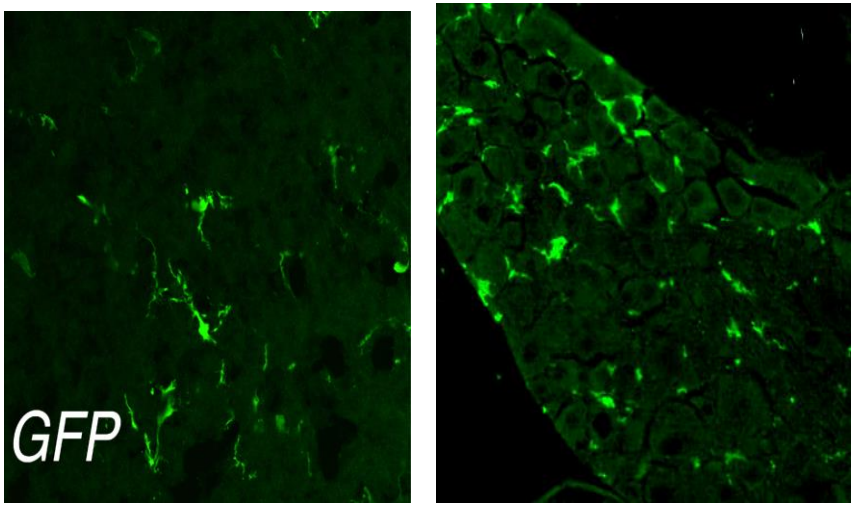
b) Cells that produce the enzyme:



yes but how to replace neurones? ***You do not need to***

Neurones uptake enzyme released by microglia that comes from the blood



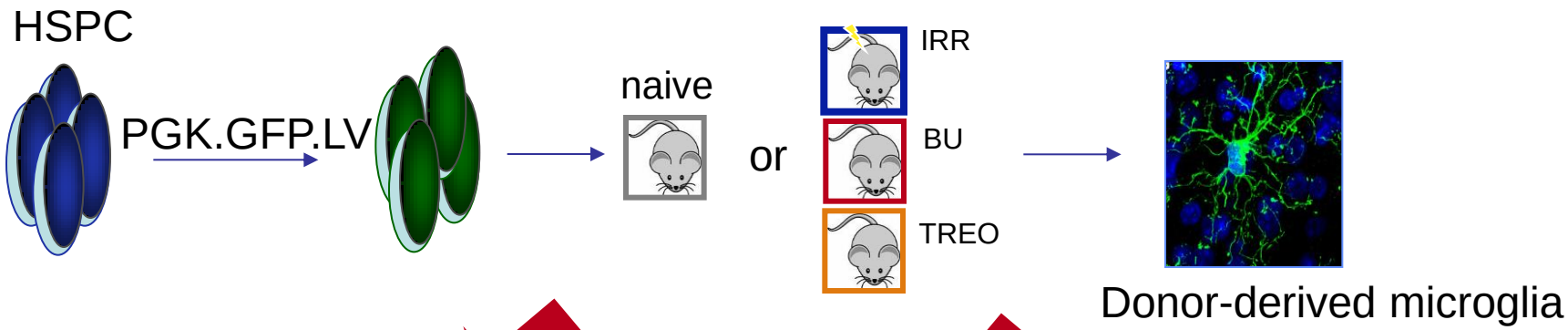


Progressive macrophage and microglia reconstitution by donor cells

Biffi et al., JCI 2004

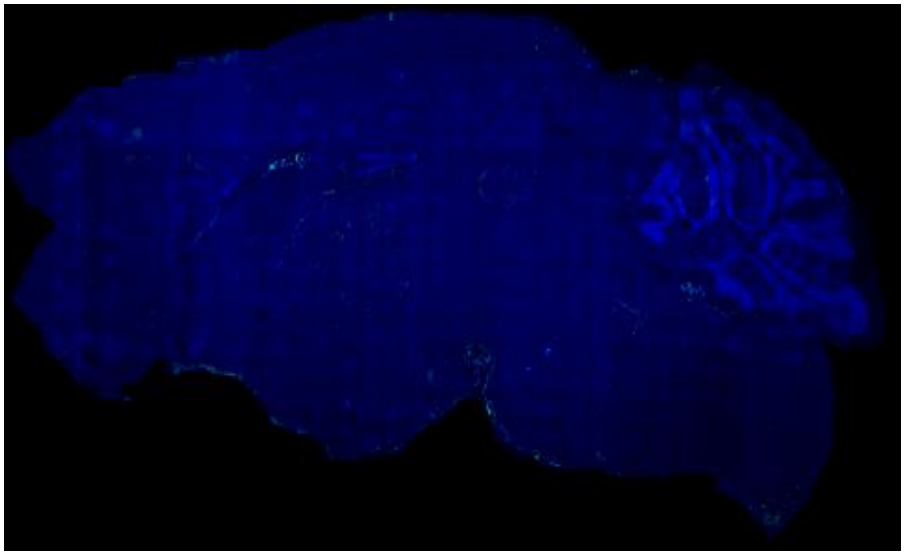
Storage removal and delivery of the functional lysosomal enzyme

The use of conditioning favours myeloid infiltration

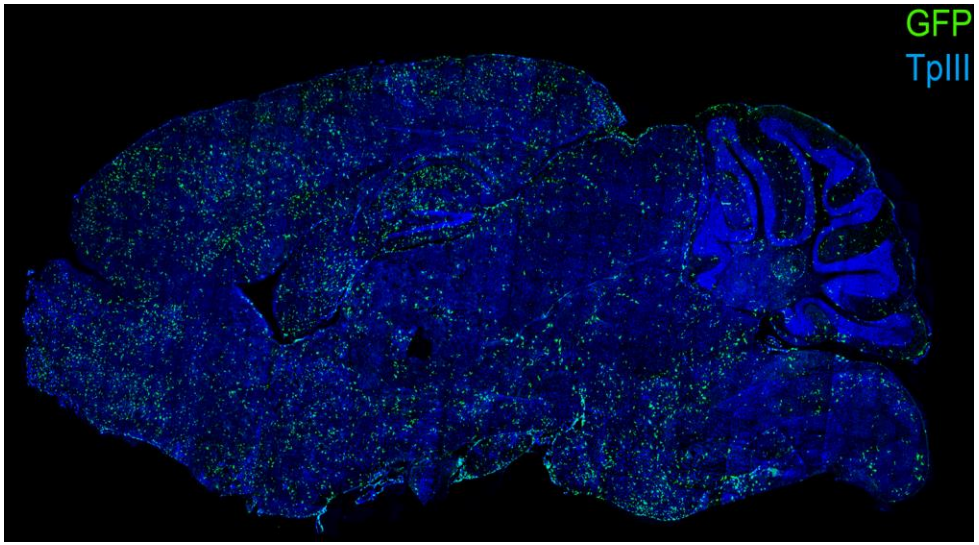


W/o conditioning

With conditioning

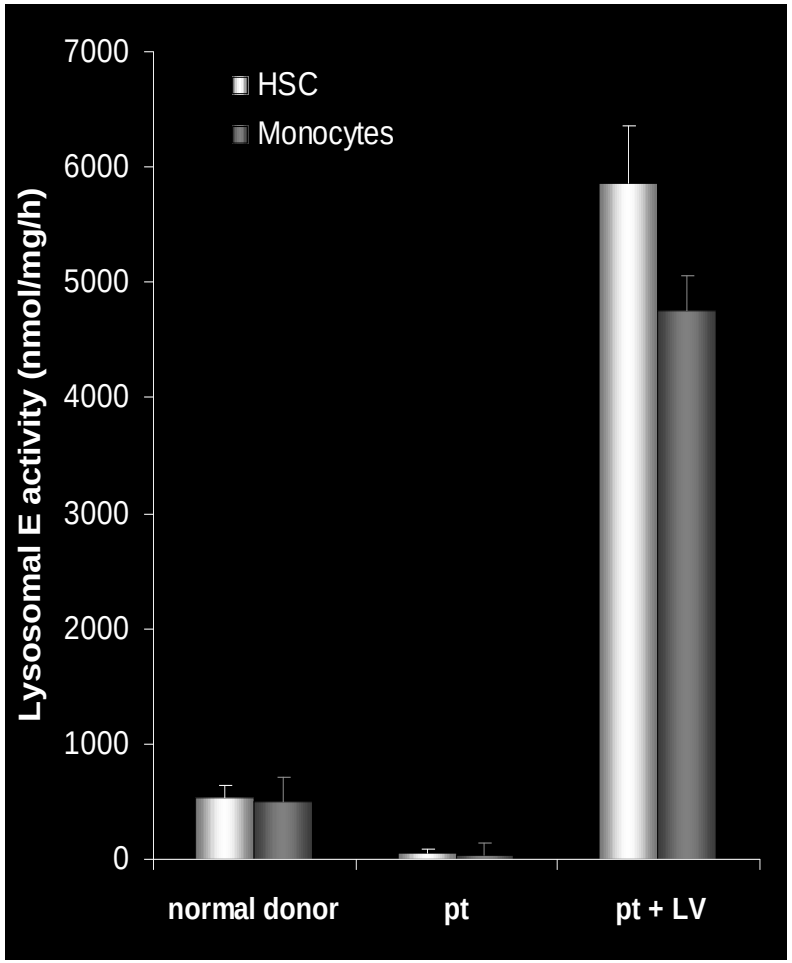


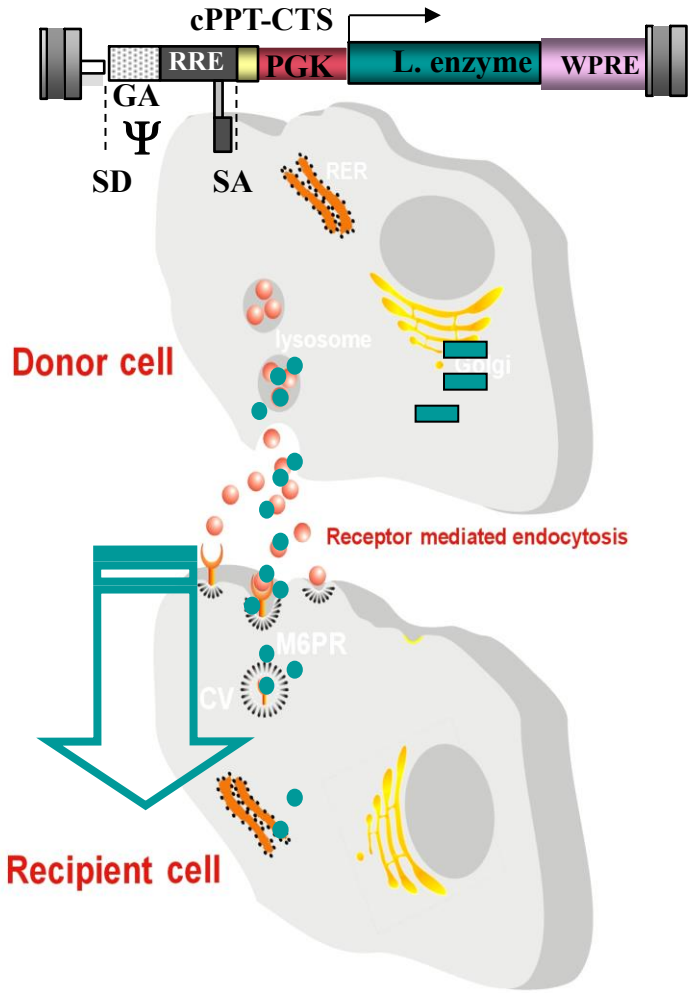
Untreated MLD mouse (+6mths from HCT)



Busulfan-treated MLD mouse (+6mths from HCT)

Gene therapy modulates enzyme





HSC gene therapy for MLD:

A Phase I/II clinical trial of hematopoietic stem cell gene therapy for the treatment of Metachromatic Leukodystrophy

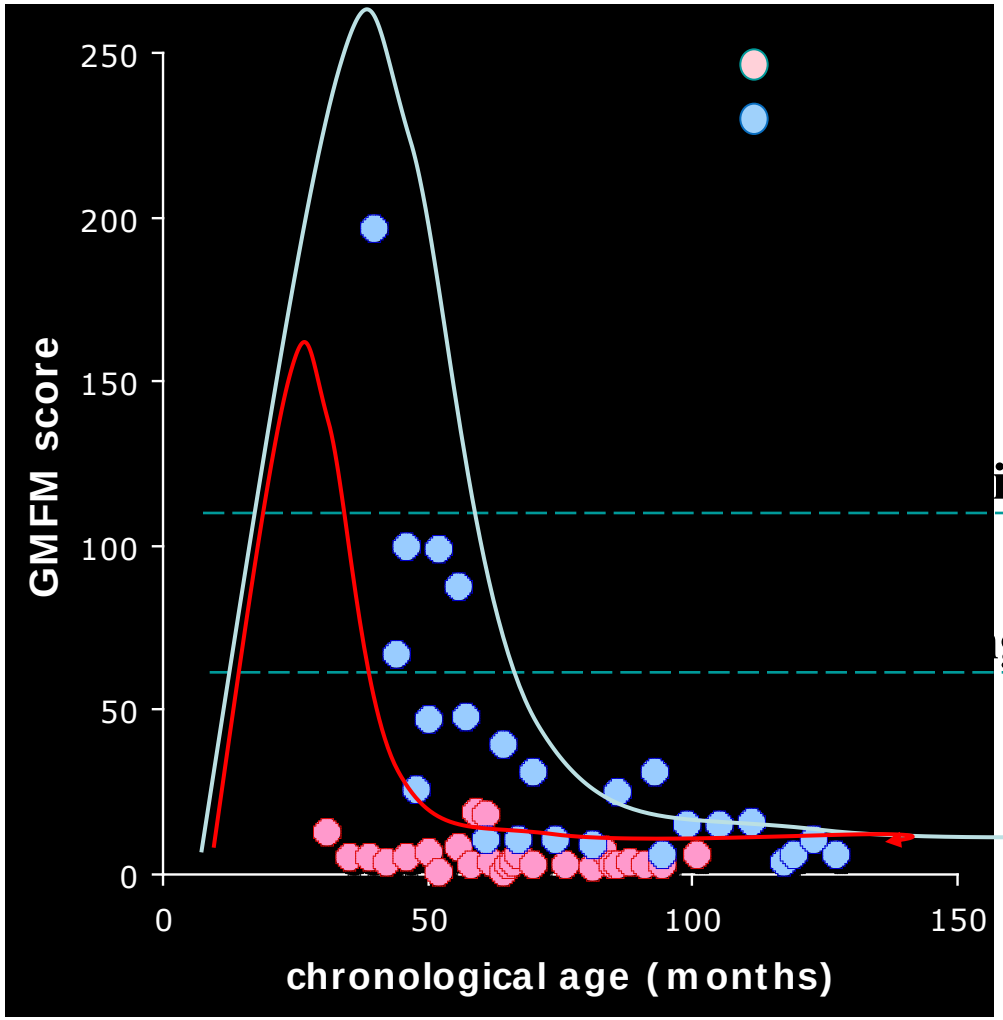
- *Autologous HSC*
- *3rd generation ARSA encoding LV*
- *Busulfan-based conditioning*

non-randomized, open label, prospective, comparative, single centre study

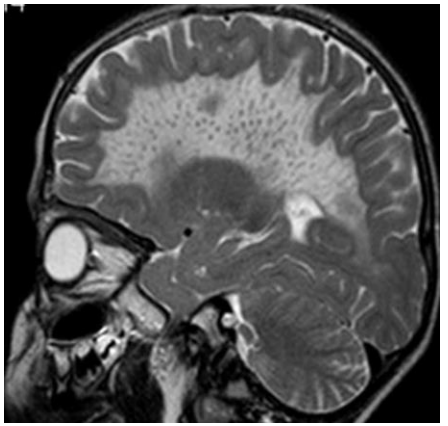
IMPD approved on March 13th, 2010
Clinical protocol approved on December 3rd, 2009

Inclusion criteria and efficacy end points

Late infantile MLD, pre-symptomatic (*n*=4)
Early juvenile MLD, pre- or early-symptomatic (*n*=4)



Late infantile (0/0)
Early juvenile (0/R)



from Biffi et al., Clin Genetics 2008

Clinical success

864 23 AUGUST 2013 VOL 341 SCIENCE www.sciencemag.org
Published by AAAS

RESEARCH ARTICLE

Lentiviral Hematopoietic Stem Cell Gene Therapy Benefits Metachromatic Leukodystrophy

Alessandra Biffi,[1,2,3]*† Eugenio Montini,[1]* Laura Lorioli,[1,2,3,4] Martina Cesani,[1] Francesca Fumagalli,[2,4,5] Tiziana Plati,[1] Cristina Baldoli,[6] Sabata Martino,[7] Andrea Calabria,[1] Sabrina Canale,[2] Fabrizio Benedicenti,[1] Giuliana Vallanti,[8] Luca Biasco,[1] Simone Leo,[9] Nabil Kabbara,[10] Gianluigi Zanetti,[9] William B. Rizzo,[11] Nalini A. L. Mehta,[12] Maria Pia Cicalese,[2,3] Miriam Casiraghi,[2] Jaap J. Boelens,[13] Ubaldo Del Carro,[5] David J. Dow,[12] Manfred Schmidt,[14] Andrea Assanelli,[3,15] Victor Neduva,[12] Clelia Di Serio,[4] Elia Stupka,[16] Jason Gardner,[17] Christof von Kalle,[14] Claudio Bordignon,[4,8] Fabio Ciceri,[3,15] Attilio Rovelli,[18] Maria Grazia Roncarolo,[1,2,3,4] Alessandro Aiuti,[1,2,3,19] Maria Sessa,[2,5] Luigi Naldini[1,4]†

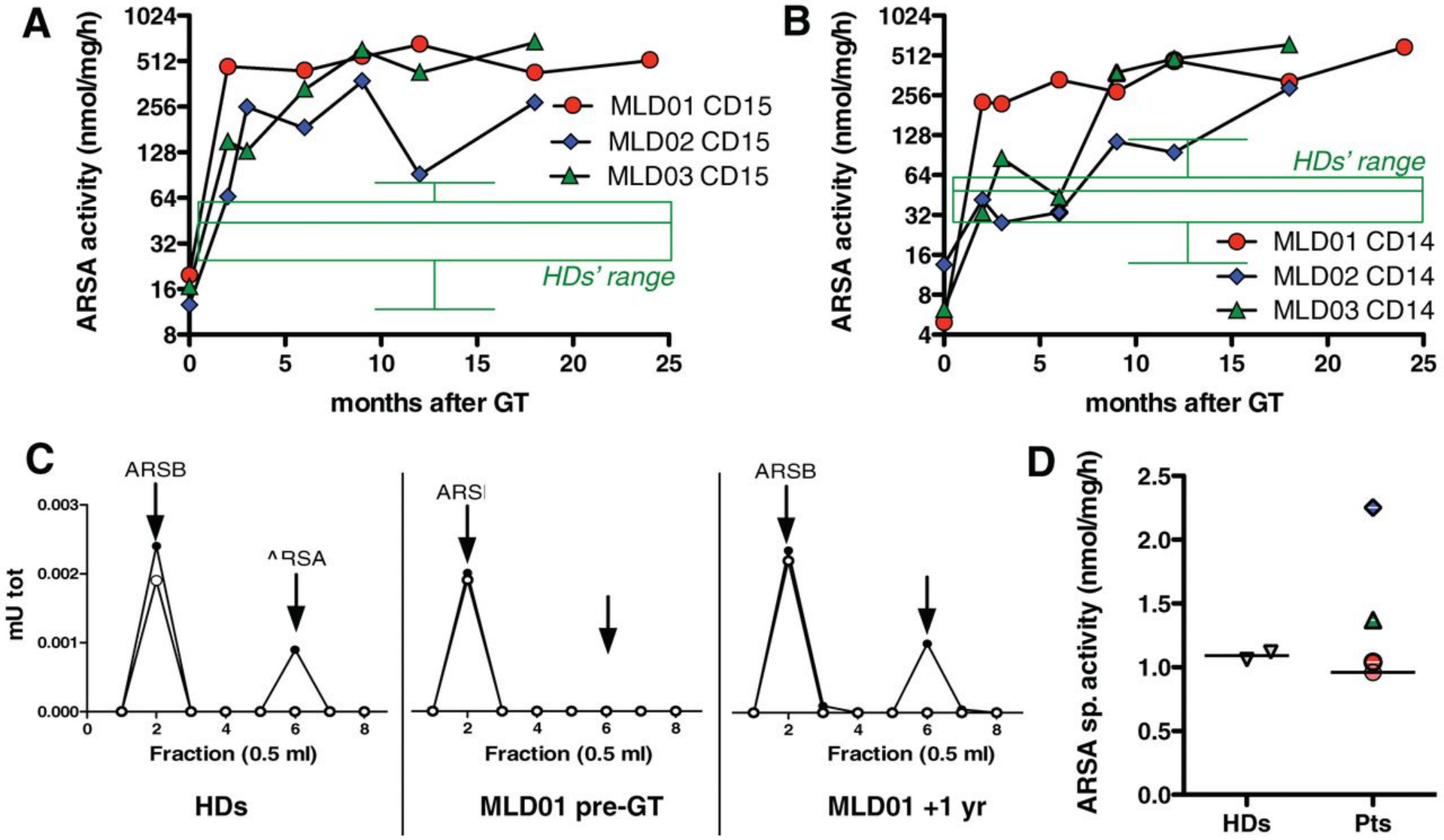
risk of genotoxic insertions because of their advanced design and the integration site selection typical of the parental HIV (*19*, *20*), it remained possible that increasing the total integration load in the infused HSPCs would offset the biosafety advantage.

In the present study, we optimized LV-mediated gene transfer into human HSCs for clinical translation and used this HSC-GT protocol to treat nine patients with early onset MLD in a phase I/II trial. Here, we report the outcome of the treatment in the first three treated patients at 24 months follow-up for patient MLD01 and 18 months follow-up for patients MLD02 and MLD03.

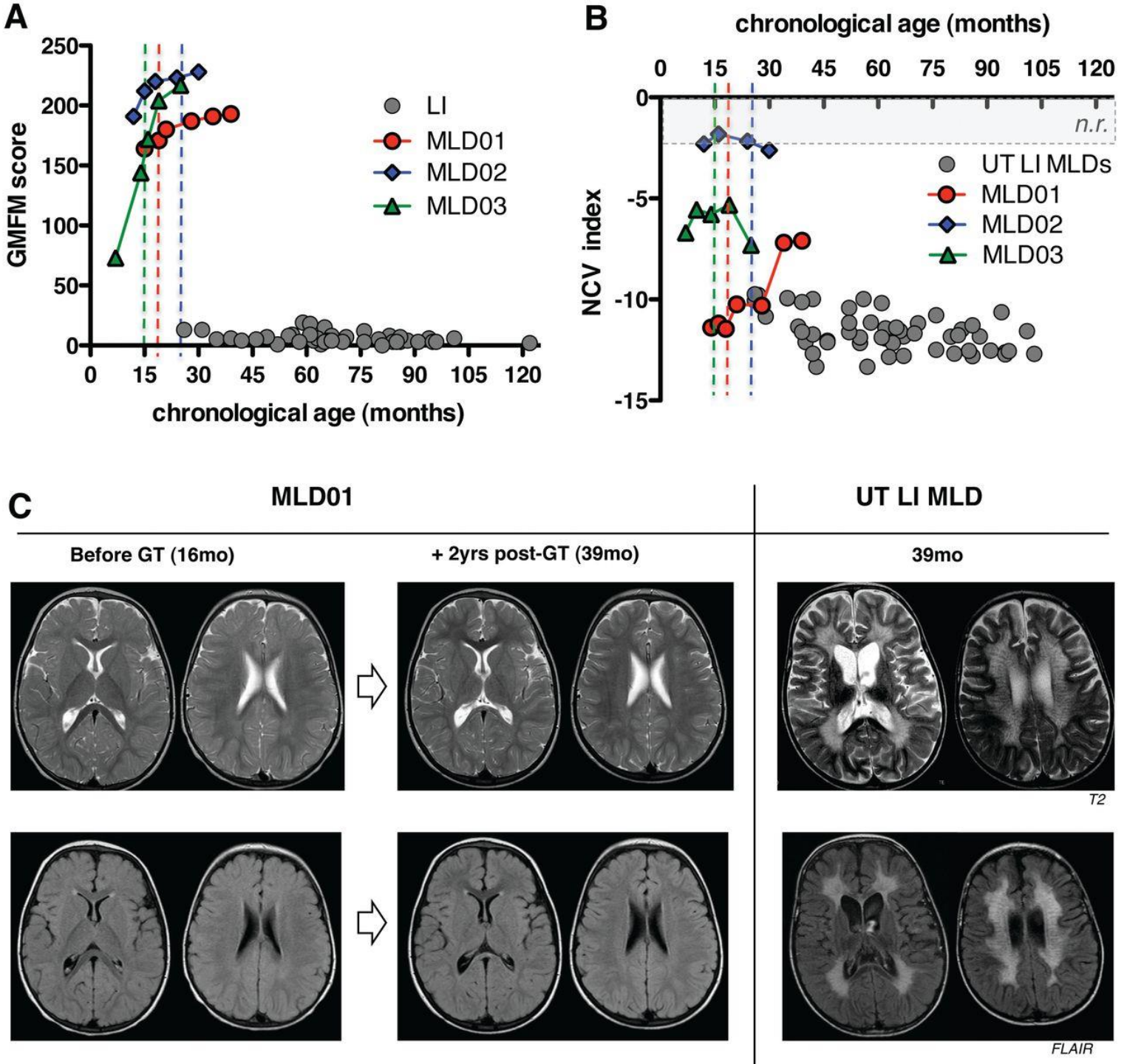
Results

Efficient ex Vivo Transfer of the ARSA *Gene into the HSPCs of MLD Patients*

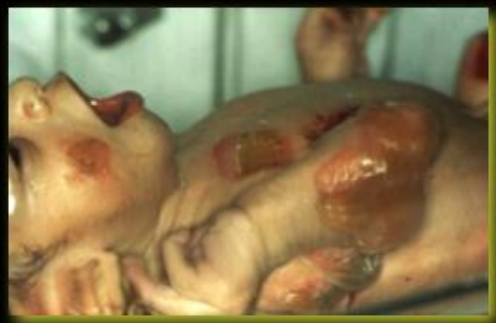
Maintenance of elevated enzyme level

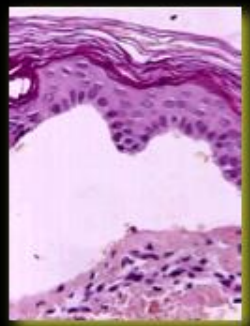


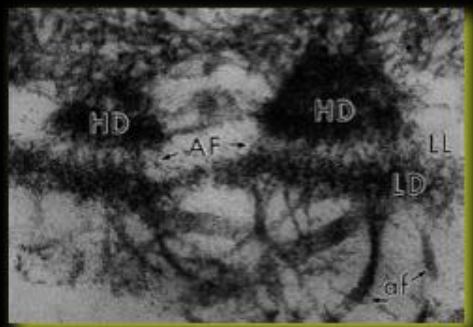
Prevention of neural degenration



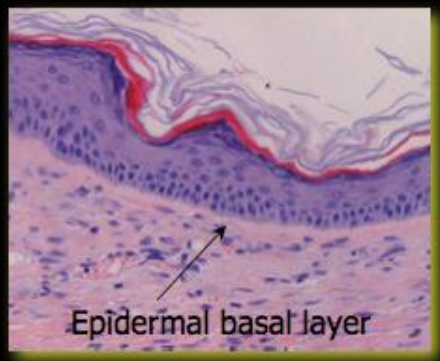
JUNCTIONAL EPIDERMOLYSIS BULLOSA

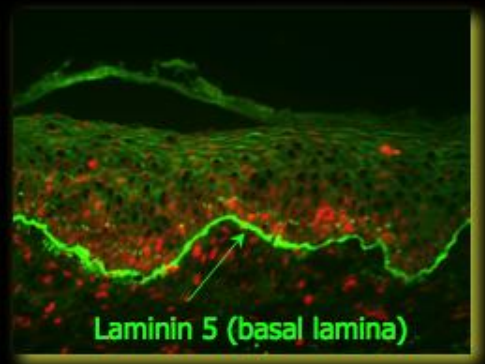


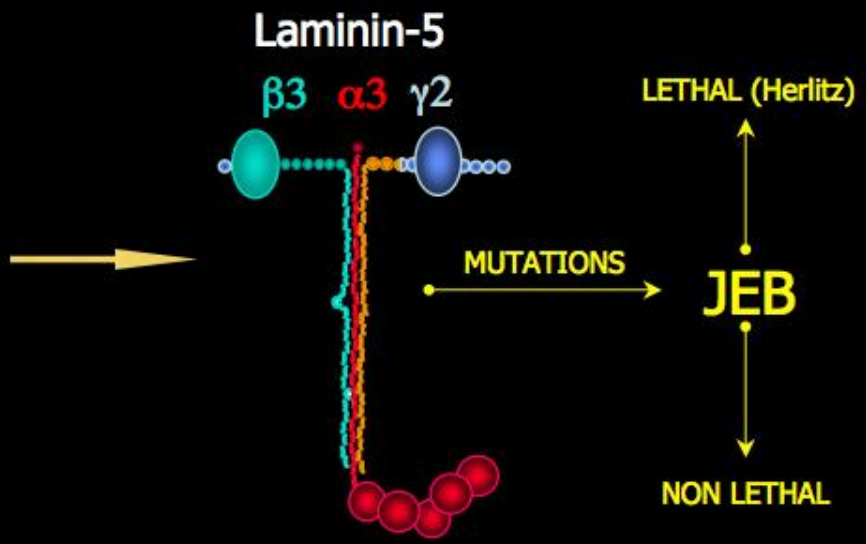




Blistering (skin, mucosa)
Dermal-epidermal separation
Abnormal hemidesmosomes



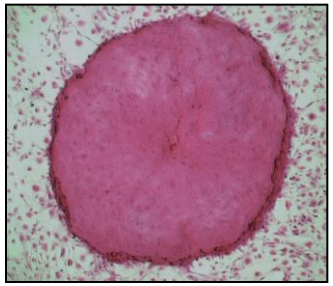




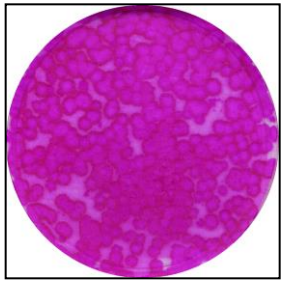
In vitro produced epidermis

1 cm^2 biopsy

holoclone

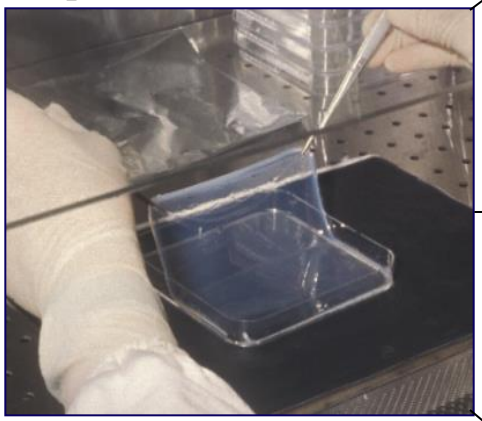


2,000-5,000 stem cells



holoclone-daughter colonies

autologous cultured epithelial sheets



Permanent epidermal regeneration in full-thickness burns covering up to 98% of the body surface.

(O' Connor, *Lancet*, 1979; Gallico, *N. Engl. J. Med.*, 1984; Pellegrini, *Transplantation* 1999; Ronfard, *Transplantation* 2000)

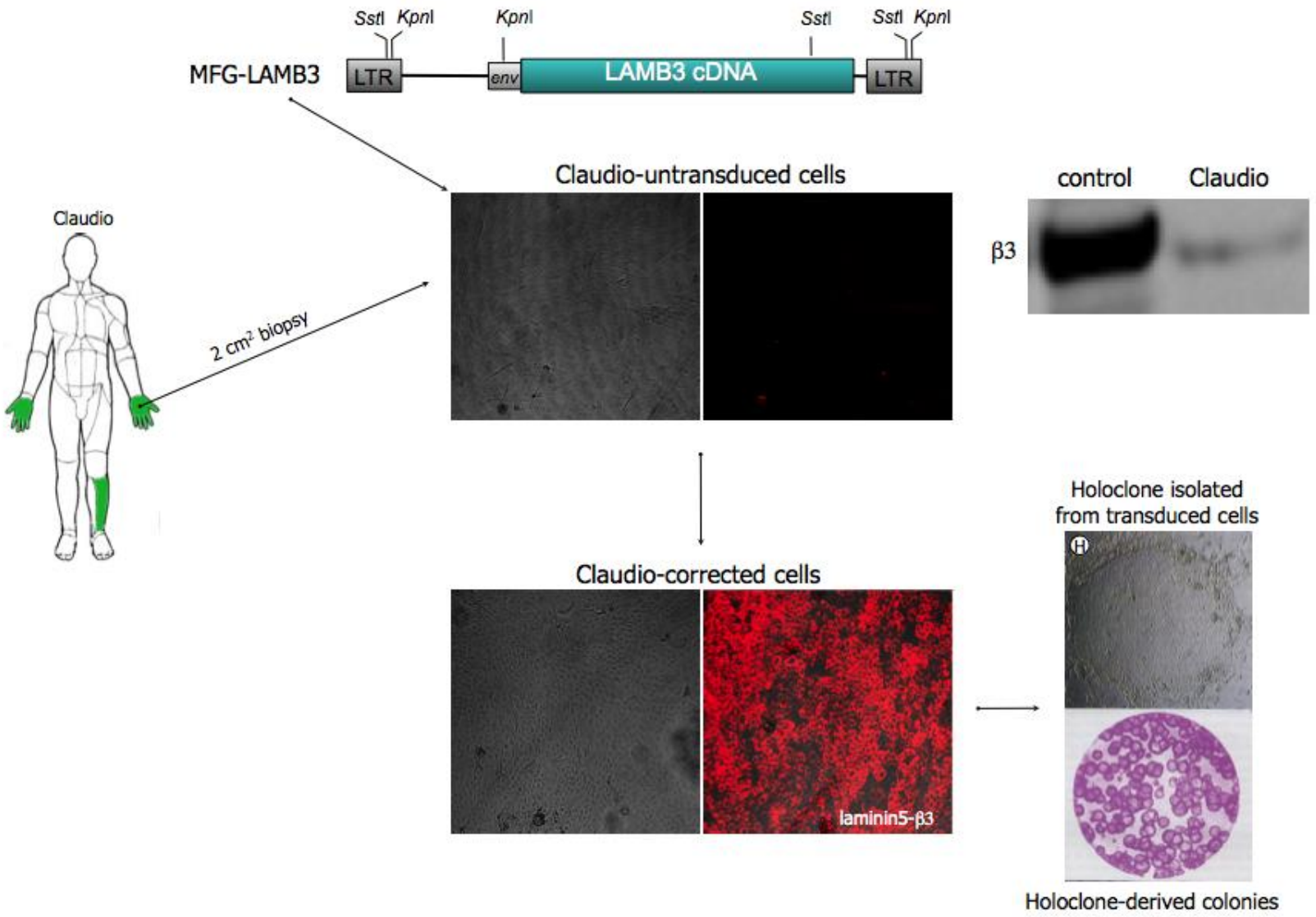
Permanent regeneration of the urethral epithelium in congenital posterior hypospadias.

(Romagnoli, *N. Engl. J. Med.*, 1990; *J. Urol.* 1993)

Repigmentation in stable vitiligo using keratinocyte/melanocyte co-cultures.

(Guerra, 2000, 2003, 2004)

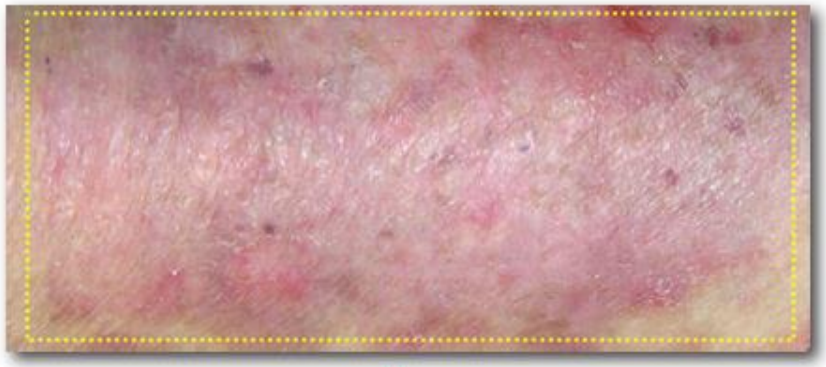
Correction of β3-defective epidermal stem cells



Mavilio et al., *Nature Medicine*, 2006, 12:1397-1402

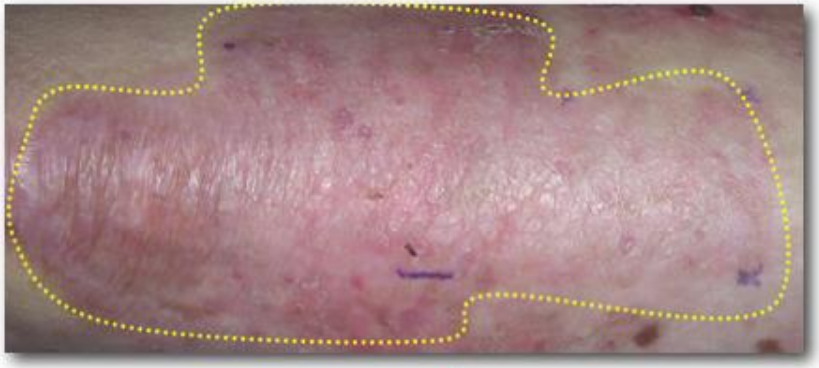
ENGRAFTMENT OF TRANSDUCED AUTOLOGOUS EPIDERMAL SHEETS

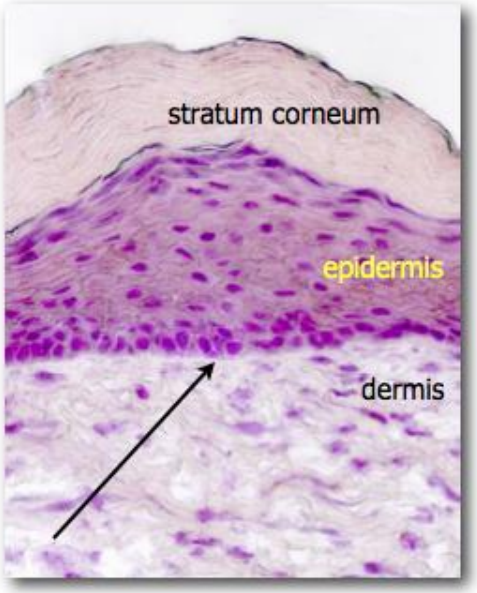
RIGHT UPPER LEG

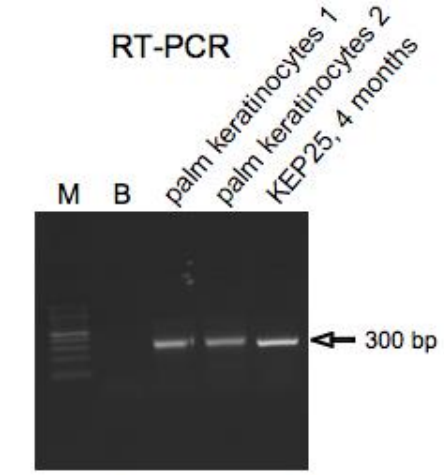


4 months

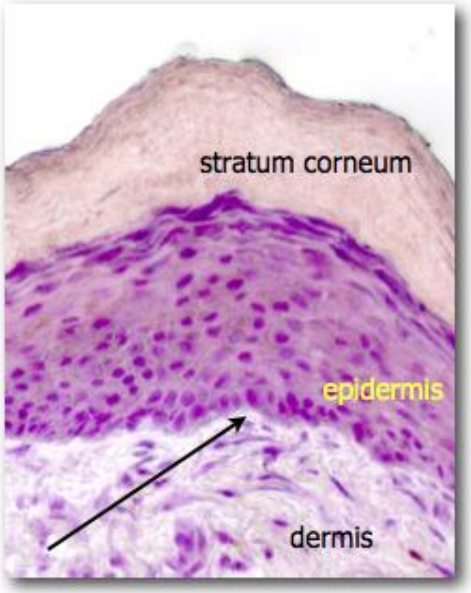
LEFT UPPER LEG







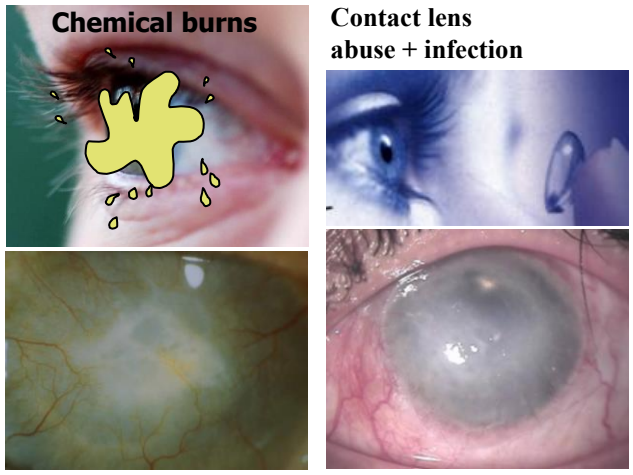
Keratin 9 (palm-specific)

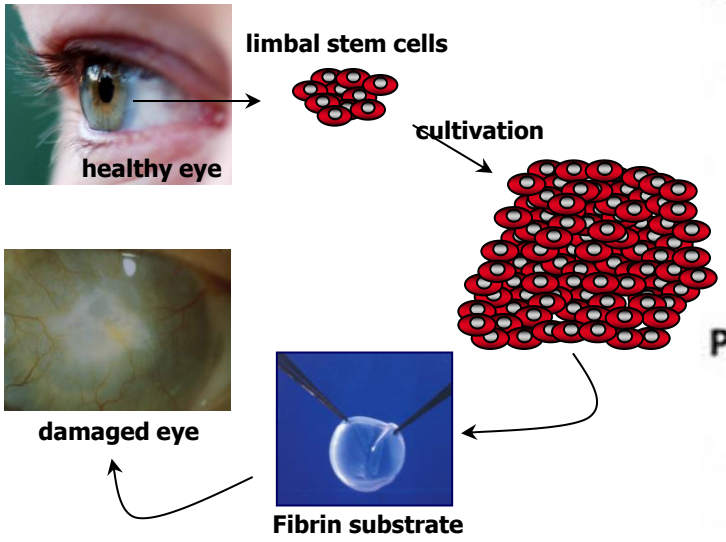


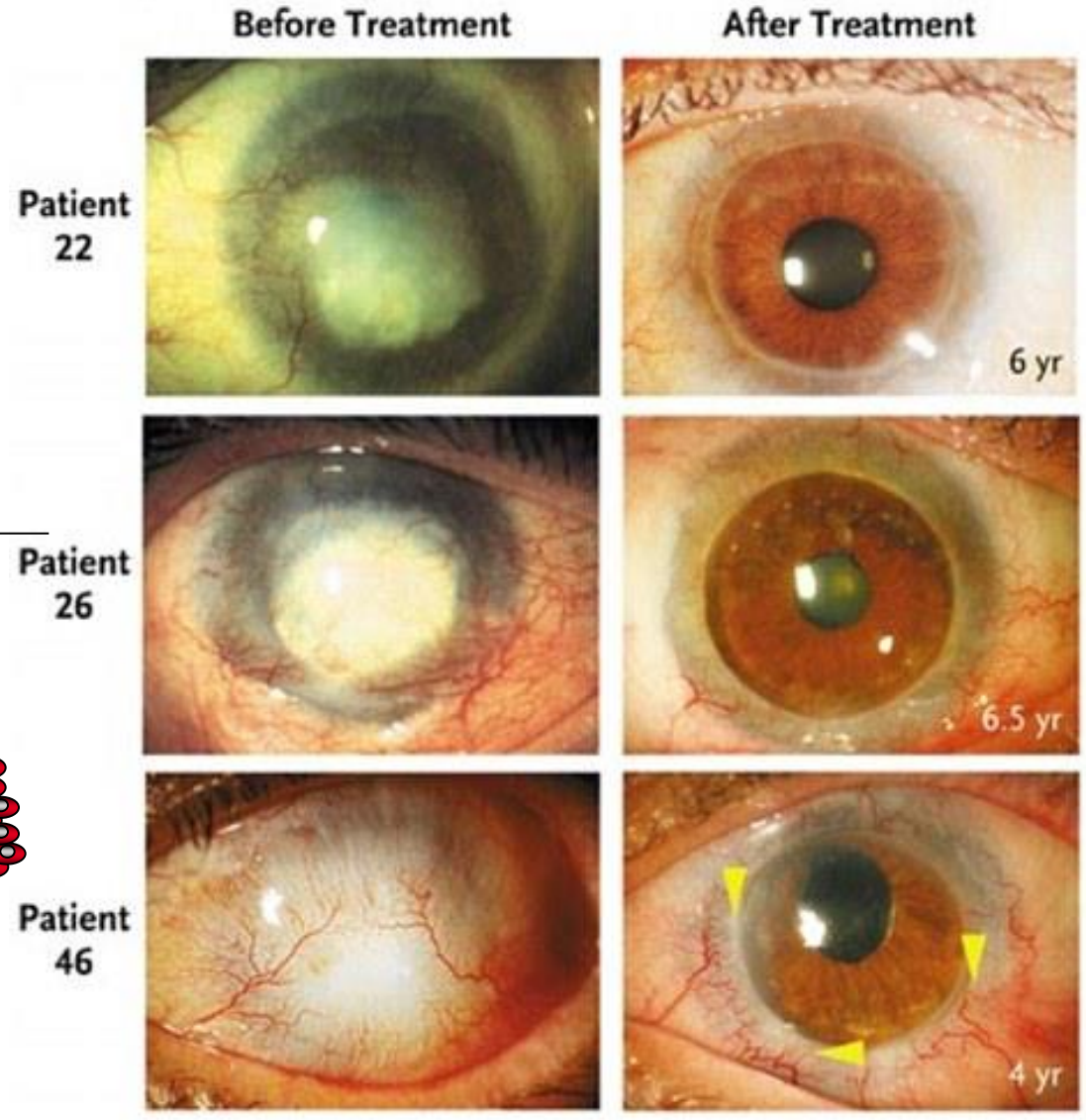
Mavilio et al., *Nature Medicine*, 2006, 12:1397-1402

Unilateral burns of the eye are “cured” with a cornea grown in vitro from stem cells isolated from the spared eye

(Rama et al NEJM 2010)







Diseases where stem cell therapy had partial, modest of no efficacy

Parkinson disease (few trials in the 90', new trials ahead)

Heart infarct (590 trials completed or ongoing)

Plethora of diseases treated with "anti-inflammatory" mesenchymal stem cells (535 trials completed or ongoing)

Muscular Dystrophy (few trials in the 90', new trials ongoing)

Severe bone fractures (35 trials completed or ongoing)

What makes the difference?

Cell therapy works with cells from the bone marrow and the epithelia (“labile tissues” as defined by Bizozzero).
These tissues can be ablated to make “space” for donor cells and have stem cells with practically unlimited self-renewal ability.
They do not “age” but the toll to pay is cancer.

Cell therapy does not work (yet) with tissues like heart, brain or muscles that cannot be ablated and thus only few donor cells can engraft. Moreover these tissues do not self renew (“perennial” according to Bizzozero) and are subject to degenerative disorders with age.

Some final ethical, economical and societal thoughts

Most of the successfully treated diseases are the best example of “personalized medicine”: one medicine for one patients only. And other treatments (e.g. gene therapy) are often mutation specific, i.e. for a subset of patients.

Most of the diseases treated so far are rare or extremely rare. They have a very high cost, even though this may be lower than life-long expensive but palliative treatments.

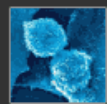
Common diseases (heart infarct) have a huge potential market, but diseases not too rare (hemophilia, cystic fibrosis, muscular dystrophy) may soon have a therapy available for thousands of patients at a cost of hundreds of thousands euros each. Who will pay for them?

Conclusions:

1. Many severe diseases have already been cured with stem cells.
2. Recently, lethal and so far “incurable” diseases have been successfully treated.
3. Many other diseases are entering clinical experimentation.
4. Each new therapy is the results of many years of pre-clinical works
5. Miracles, on the other hand are rare and those who promise a cure for any disease should provide unequivocal evidence of efficacy.

CELL MEDICINE

DEDICATED TO THE ADVANCEMENT OF ADULT STEM CELLS FOR THE TREATMENT OF HUMAN DISEASES.



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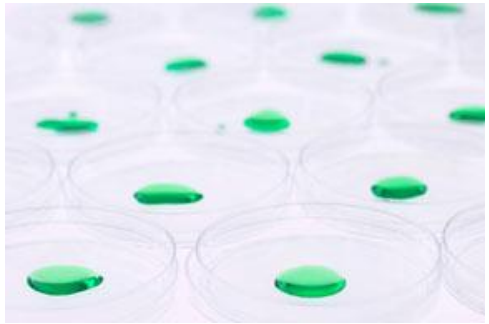

FOR INFORMATION ABOUT STEM CELL TREATMENT:

CALL (800) 980-STEM

+1 954-636-3390

(FROM OUTSIDE NORTH AMERICA)

Stem Cell Therapy is Available Now Outside the US and Canada

Cell Medicine arranges stem cell therapy for patients with the following conditions:

- Autoimmune Diseases
- Cerebral Palsy
- Critical Limb Ischemia
- Degenerative Joint Disease
- Diabetes Type 2
- Heart Failure
- Multiple Sclerosis
- Osteoarthritis
- Rheumatoid Arthritis
- Spinal Injury

Treatment is only available outside the US and Canada and is not covered by most insurance.

Treatment With Your Own Stem Cells

Adult stem cells can be harvested from many areas of the body, including the bone marrow, fat and peripheral blood. Once the cells have been harvested, they are sent to the lab where they are purified and assessed for quality before being reintroduced back in the patient. Since the stem cells come from the patient there is no possibility for rejection.

Adult Stem Cells

Cell Medicine advocates the use of autologous stem cells as they have no ethical or moral issues and pose no possibility for rejection since they come from the patient. According to various studies, stem cells isolated from a patient (i.e. from the bone marrow or fat) have the ability to become different cell types (i.e. nerve cells, liver cells, heart cells and cartilage cells). Studies have also shown that these are capable of "homing in" on and repairing damaged tissue.

Cell Medicine only advocates the use of stem cells derived from the non-controversial sources: bone marrow, muscle, skin, fat and blood.

Click here for the patient application

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Homepage

Benvenuti

È con grande piacere che vi presentiamo il mondo della terapia Cellvital. Vi invitiamo a dedicare alcuni minuti al Vostro Capitale Salute.

La terapia Cellvital rappresenta una tappa importante nello sviluppo della medicina naturale e biologica. Resta la prerogativa esclusiva dell'Health Center Clinique Lémana, centro di salute di fama mondiale, stimato per il suo rigore scientifico.

Il nostro metodo Cellvital è una medicina preventiva nata in Svizzera che si adatta alle vostre esigenze specifiche.

Da più di 50 anni, restiamo fedeli alla nostra filosofia :

**« Non pensiamo di aggiungere anni alla vostra vita,
ma di dare qualità di vita ai vostri anni »**

Denise de Loë-Pfister
Direttore Generale

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LATEST NEWS

Beike Biotech

Tomorrow's Treatments Today

Welcome to Beike Biotechnology. Beike Biotechnology is a leading biotech company focused on adult stem cell technologies for treating incurable diseases. We are contracted to provide stem cells to 27 hospitals worldwide where over 250 patients are treated monthly with our products.

At this website you will find information about our company and about treatments available to international patients.

Safety is our number one priority. Our stem cell products are provided exclusively to the leading hospitals certified to carry out our stringent protocols. Beike selects hospitals based on five key criteria: the hospital's environment, doctor certification, cost, reputation as well as excellence of rehabilitation staff and facilities.

READ MORE...

Updates to Past Press Release

Monday, 11 May 2009 20:49

Beike Biotechnology would like to issue two updates to a past press releases: Stem Cell Leader Beike Signs 8 New Cooperation Agreements, Establishes Safety Monitoring Board

Note: Special Appreciation goes to Medical Journalist Fabio Turone for his support to ensure the information on this web site is accurate.

READ MORE...

Stem Cell Therapy Today in the People's Republic

Regenecell®
Bringing bioscience to life™

हिन्दी

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Bringing Bioscience to Life

Stem cell therapy is an important new area of medicine with the potential of offering viable therapeutic options for debilitating degenerative disease and injury.

Regenecell was founded with the mission of becoming a leader in the field - affording patients the very best regenerative treatments that biology and science have to offer.

We are committed to bringing the benefits of bioscience to our patients, by providing umbilical stem cells of the highest quality possible.

Treatment is delivered by medical practitioners who are guided by strict protocols, ensuring an uncompromising level of quality care for an optimal outcome.

Come valutare e non cadere in trappole?

Regola n° 1: il sito deve contenere informazioni dettagliate su quali cellule staminali vengono utilizzate

Regola n° 2: Se il sito promette la cura di molte malattie diverse tra loro, la cosa è sospetta

Regola n° 3: Il responsabile della clinica deve avere pubblicato gli studi alla base dei suoi metodi su note riviste internazionali.

Regola n° 4: i costi devono essere dettagliati.

Antonio Pigafetta

Assistant and Navigator of Ferdinand Magellan

“Noi non conosciamo la via della ritirata”

Collaborators:

S.C.R.I. (Dibit, HSR, Milan)
Maurilio Sampaolesi (α-SGC ko/GRMD)
Anna Innocenzi (Histochemistry)
Rossana Tonlorenzi (Cell culture)
Beatriz Galvez (Homing)
Arianna Dellavalle (Pericytes)
Sara Benedetti (Immortalization)
Saverio Tedesco (Dys-HAC)
Graziella Messina (Lentivector)
Cesare Gargioli (Old muscle)

Washington University
Jeffrey Chamberlain (micro-dystrophin)

University of Modena
Stefano Ferrari (micro-array)
Enrico Tagliafico

Ecole Veterinarie Mason Alfort
Stephane Blot (dogs)
Nicolas Gringer

University of Pavia
Roberto Bottinelli, (physiology)
Giuseppe D' Antona

University of Milan
Yvan Torrente (patients)

Tottori University
Mitsuo Oshimura (HAC)

EPFL Lausanne
Didier Trono (floxed lenti)

UT South Western Medical Center
Woody Wright (Tert)