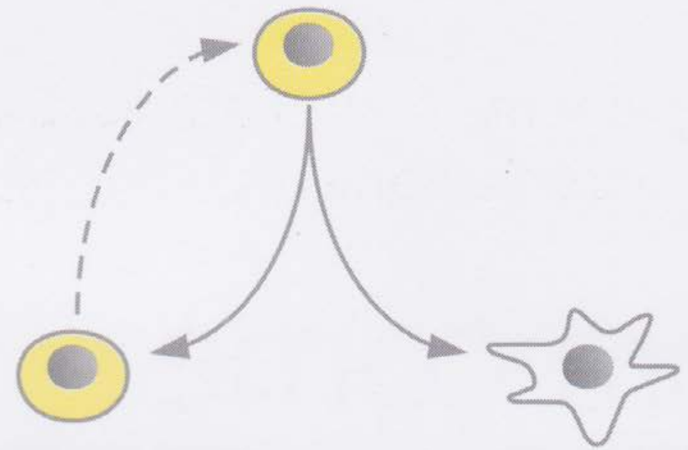
Che cos'è una cellula staminale

Sandra Zecchi-Orlandini

Dipartimento di Medicina sperimentale e clinica

Sezione di Anatomia e Istologia.

Università di Firenze

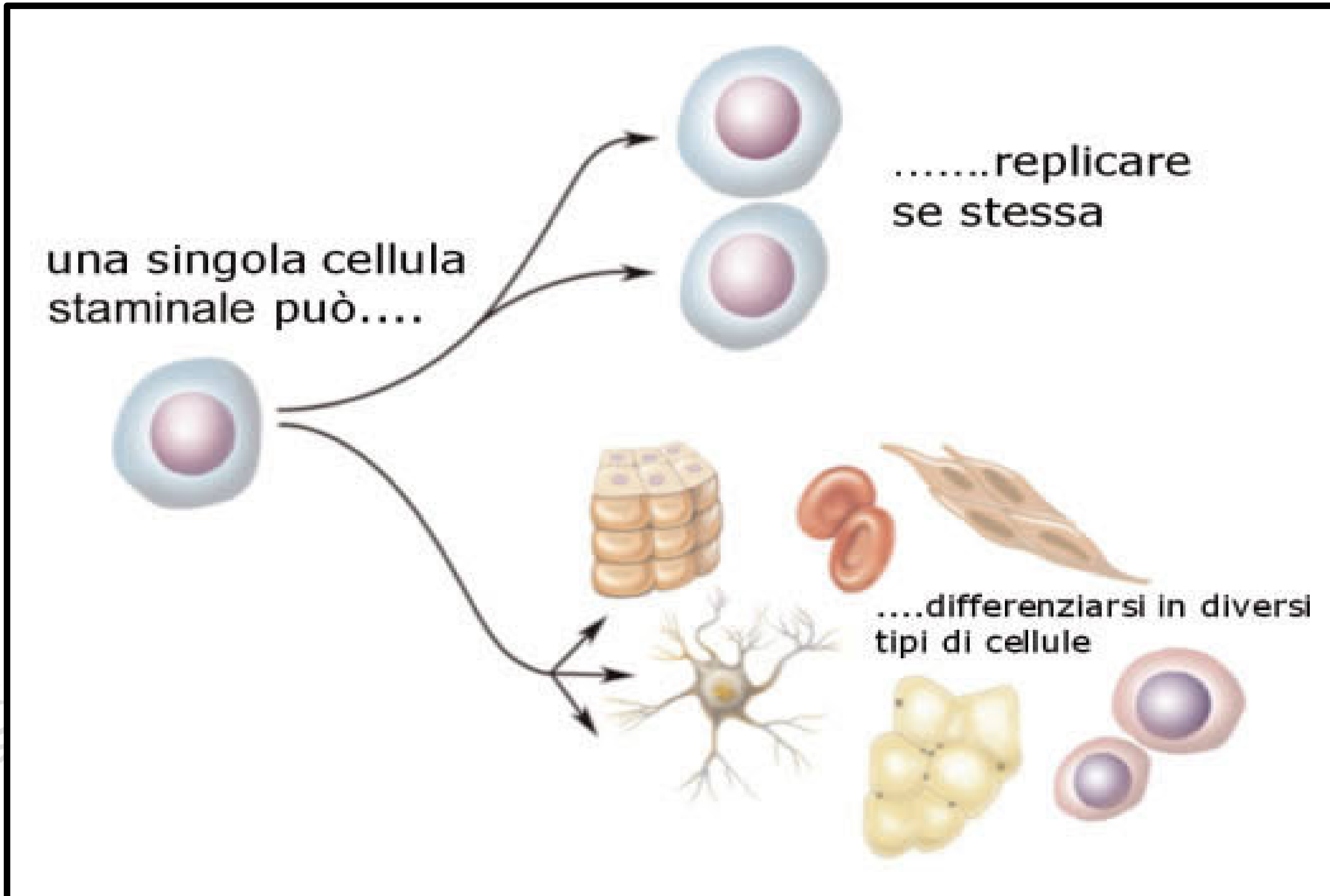


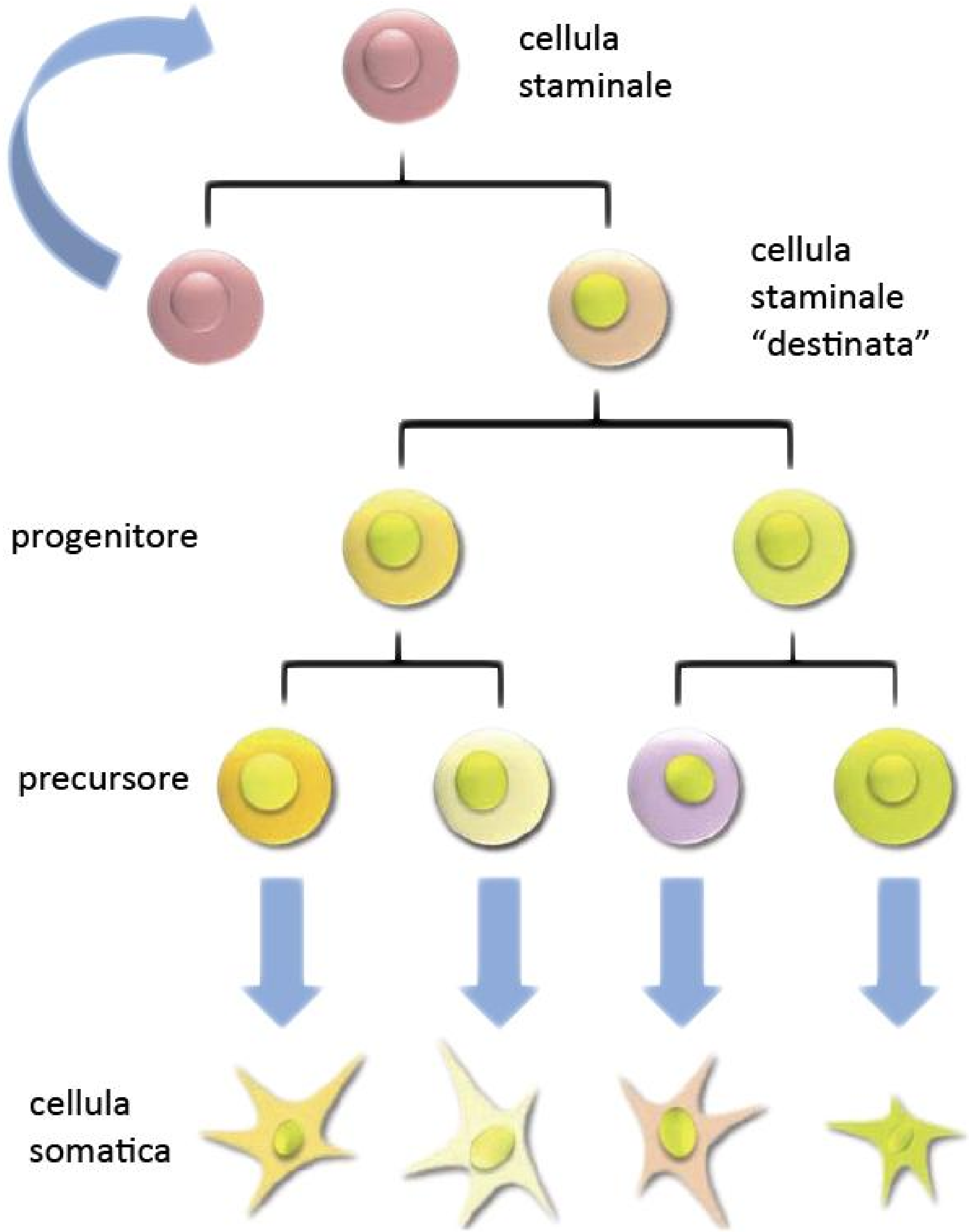
Autorinnovamento

capacità di crescere ed espandersi

Differenziazione

capacità di crescere in tipi diversi di cellule


una singola cellula
staminale può....
.......replicare
se stessa
....differenziarsi in diversi
tipi di cellule



http://www.iss.it/binary/publ/cont/Dispensa_11_1_web.pdf

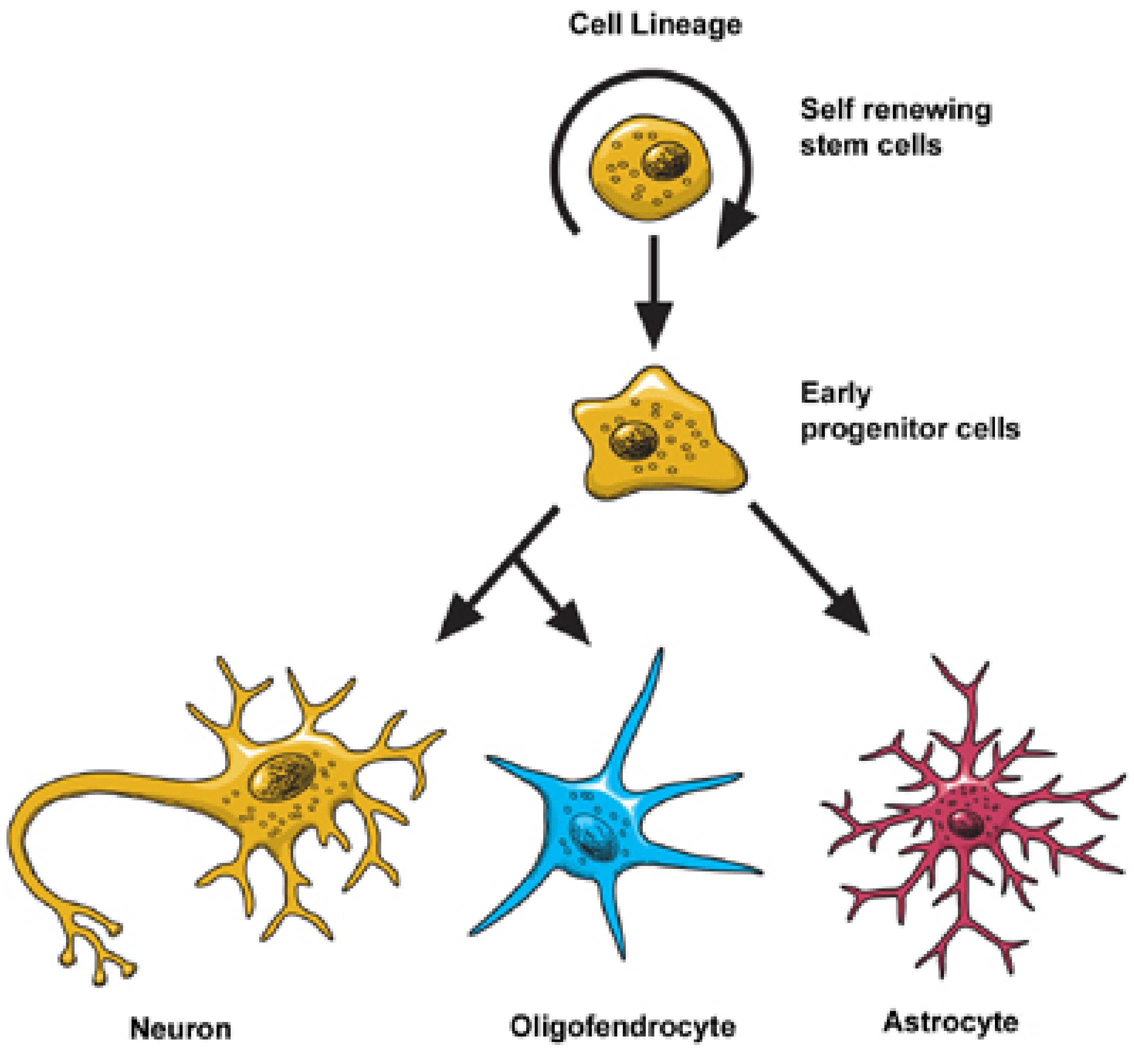
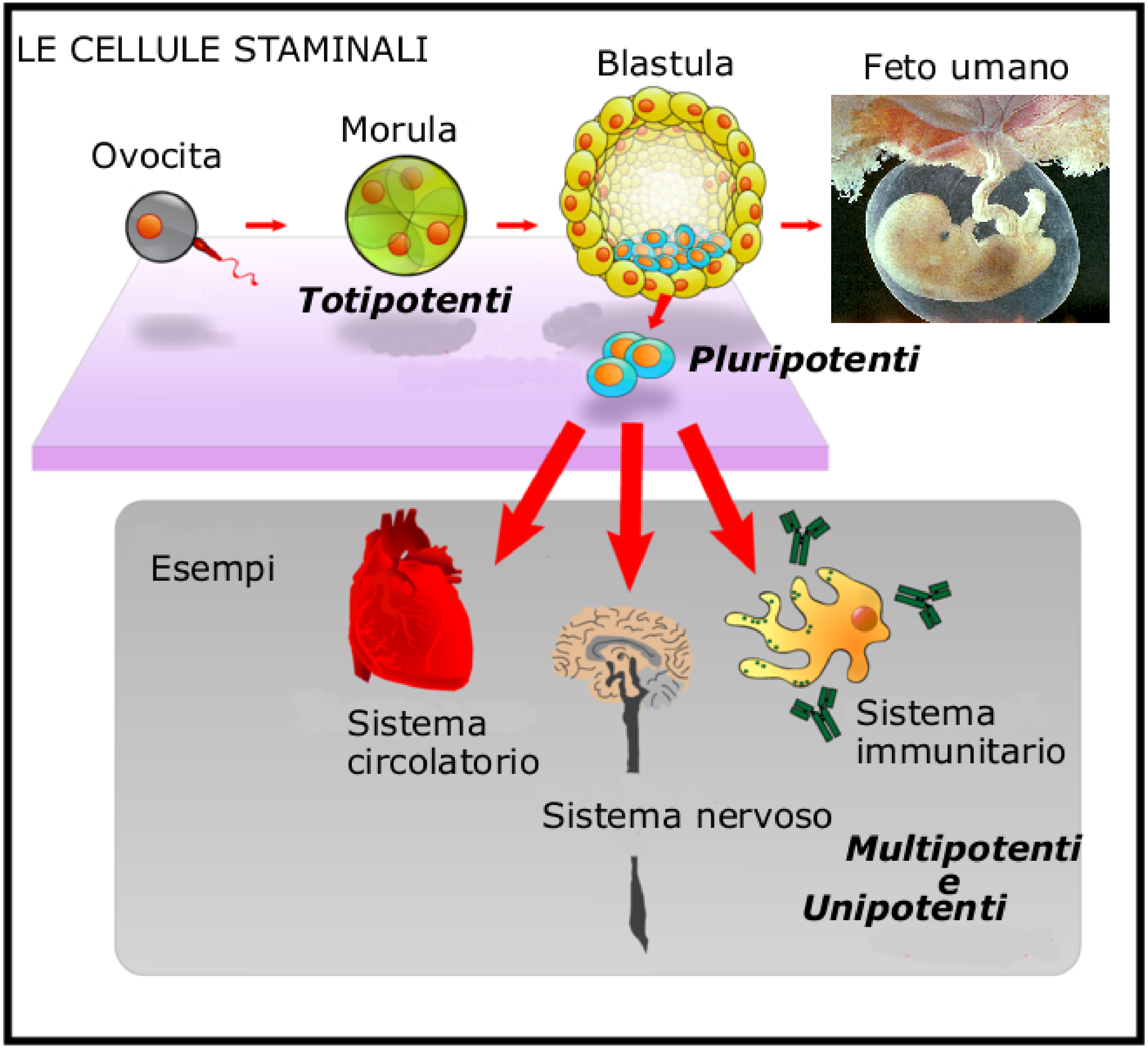
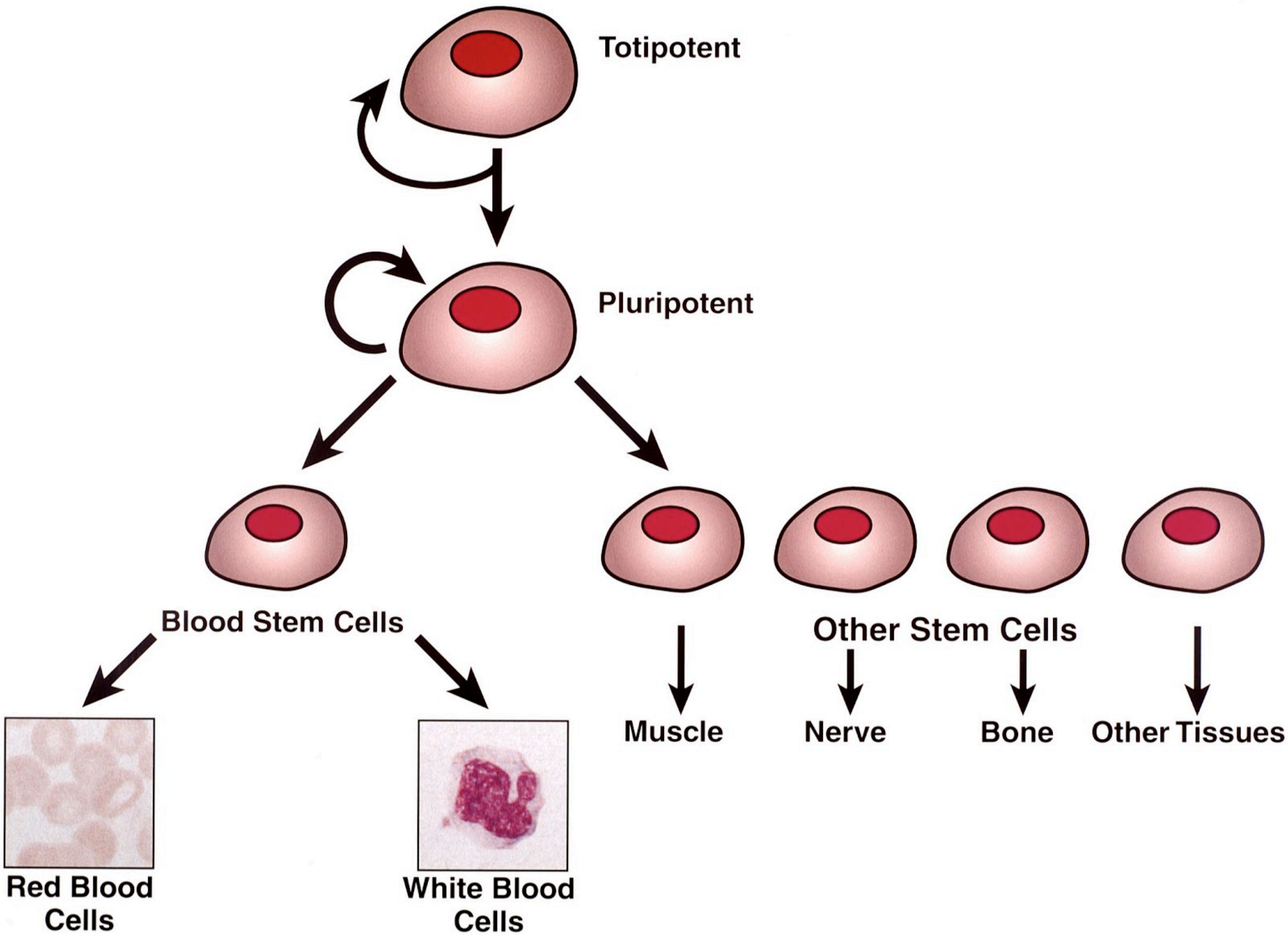

Cell Lineage
Self renewing
stem cells
Early
progenitor cells
Neuron
Oligofendrocyte
Astrocyte

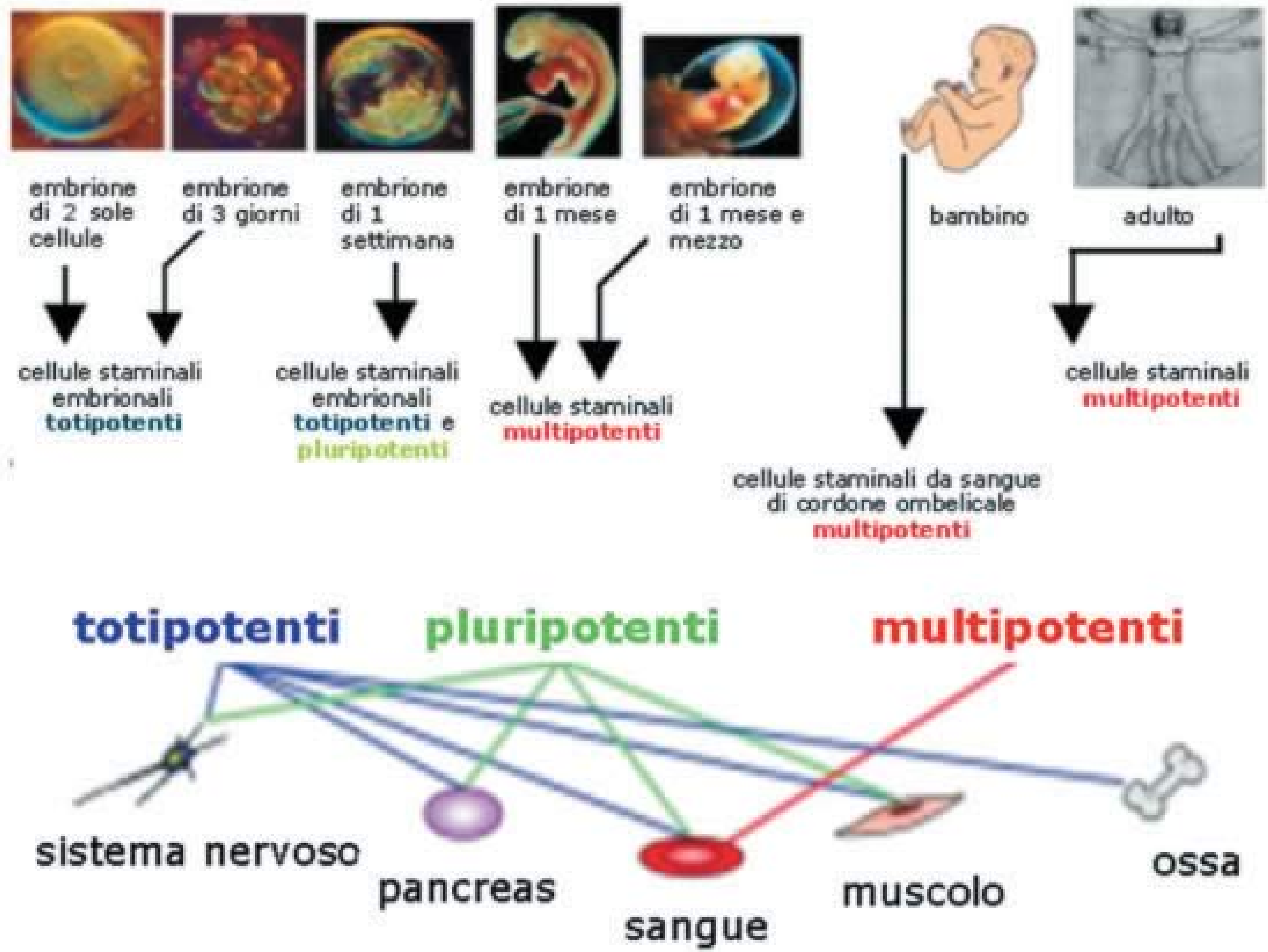
Tabella 1 - *Potenziale differenziativo e caratteristiche funzionali dei diversi tipi di cellule staminali.*

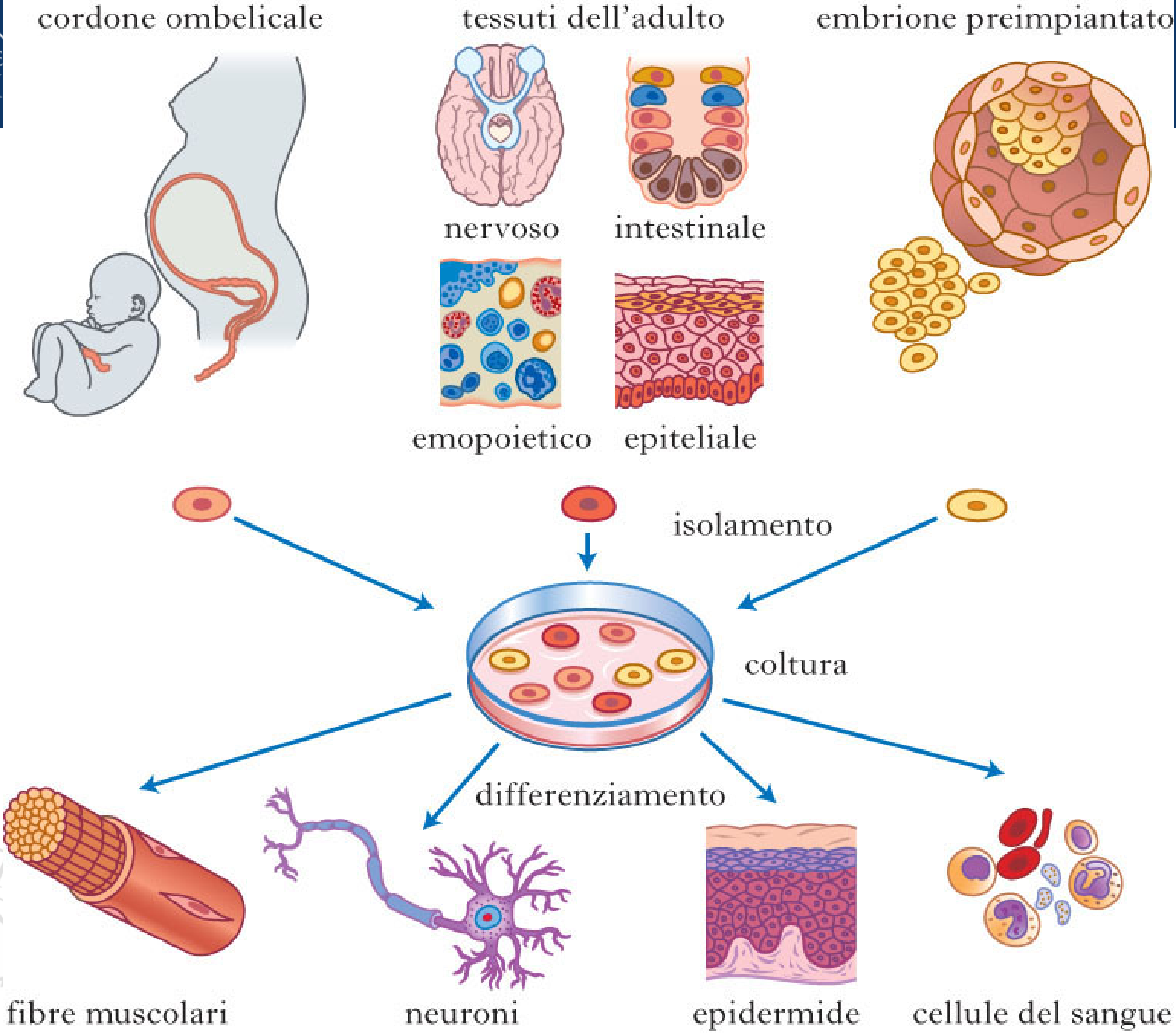
Tipo di cellula staminale	Sorgente	Potenziale differenziativo	Caratteristiche funzionali
Cellula staminale embrionale	Zigote e cellule derivate fino allo stadio di 8 blastomeri	Totipotente	Cellule in grado di riprodursi in modo virtualmente indefinito mantenendo il proprio stato altamente indifferenziato. Possono dare origine a qualsiasi tipo di tessuto embrionale (ectoderma, mesoderma ed endoderma) ed extraembrionale (annessi embrionali), quindi sono in grado di dare origine ad un individuo.
	Embrioblasti e cellule germinali primordiali	Pluripotente	Cellula in grado di riprodursi in modo virtualmente indefinito mantenendo il proprio stato altamente indifferenziato. Può dare origine a qualsiasi tipo di tessuto embrionale (ectoderma, mesoderma ed endoderma) ma non agli annessi embrionali.
Cellula staminale somatica	Cellule dei tessuti fetali, del cordone ombelicale, del midollo osseo e di vari altri tessuti nell'adulto.	Multipotente	Cellula in grado di riprodursi in modo non indefinito mantenendo il proprio stato indifferenziato. Può dare origine a cellule dello stesso e di altri tessuti, ma non tutti (cellule staminali ematopoietiche, cellule staminali mesenchimali).
		Unipotente	Cellula in grado di riprodursi in modo non indefinito mantenendo il proprio stato indifferenziato. Può dare origine ad uno specifico tipo di cellula matura (cellule dello strato germinativo dell'epidermide, cellule del limbo corneale).
	Cellule staminali indotte (iPSC)	Pluripotente	Cellula in grado di riprodursi in modo virtualmente indefinito mantenendo il proprio stato altamente indifferenziato, grazie alla riprogrammazione in vitro di cellule somatiche mature umani (fibroblasti). Può dare origine a qualsiasi tipo di tessuto.

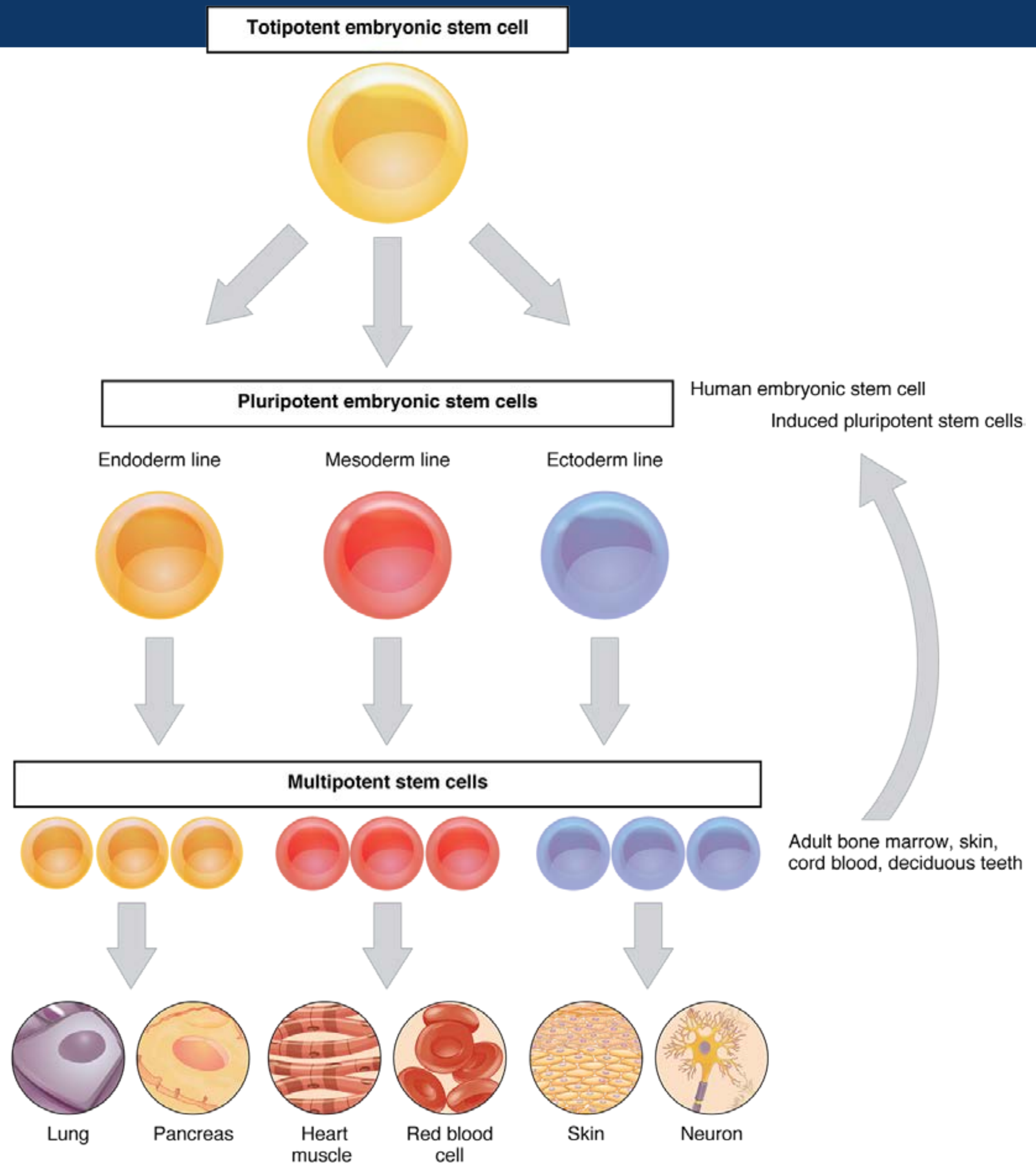

LE CELLULE STAMINALI
Ovocita
Morula
Blastula
Feto umano
Totipotenti
Pluripotenti
Esempi
Sistema circolatorio
Sistema nervoso
Sistema immunitario
Multipotenti
e
Unipotenti

Hierarchy of Stem Cells




embrione di 2 sole cellule
embrione di 3 giorni
embrione di 1 settimana
embrione di 1 mese
embrione di 1 mese e mezzo
bambino
adulto
cellule staminali embrionali totipotenti
cellule staminali embrionali totipotenti e pluripotenti
cellule staminali multipotenti
cellule staminali da sangue di cordone ombelicale multipotenti
cellule staminali multipotenti
totipotenti
pluripotenti
multipotenti
sistema nervoso
pancreas
sangue
muscolo
ossa


cordone ombelicale
tessuti dell'adulto
embrione preimpiantato
nervoso
intestinale
emopoietico
epiteliale
isolamento
coltura
differenziamento
fibre muscolari
neuroni
epidermide
cellule del sangue


Totipotent embryonic stem cell
Pluripotent embryonic stem cells
Human embryonic stem cell
Induced pluripotent stem cells
Endoderm line
Mesoderm line
Ectoderm line
Multipotent stem cells
Adult bone marrow, skin,
cord blood, deciduous teeth
Lung
Pancreas
Heart
muscle
Red blood
cell
Skin
Neuron

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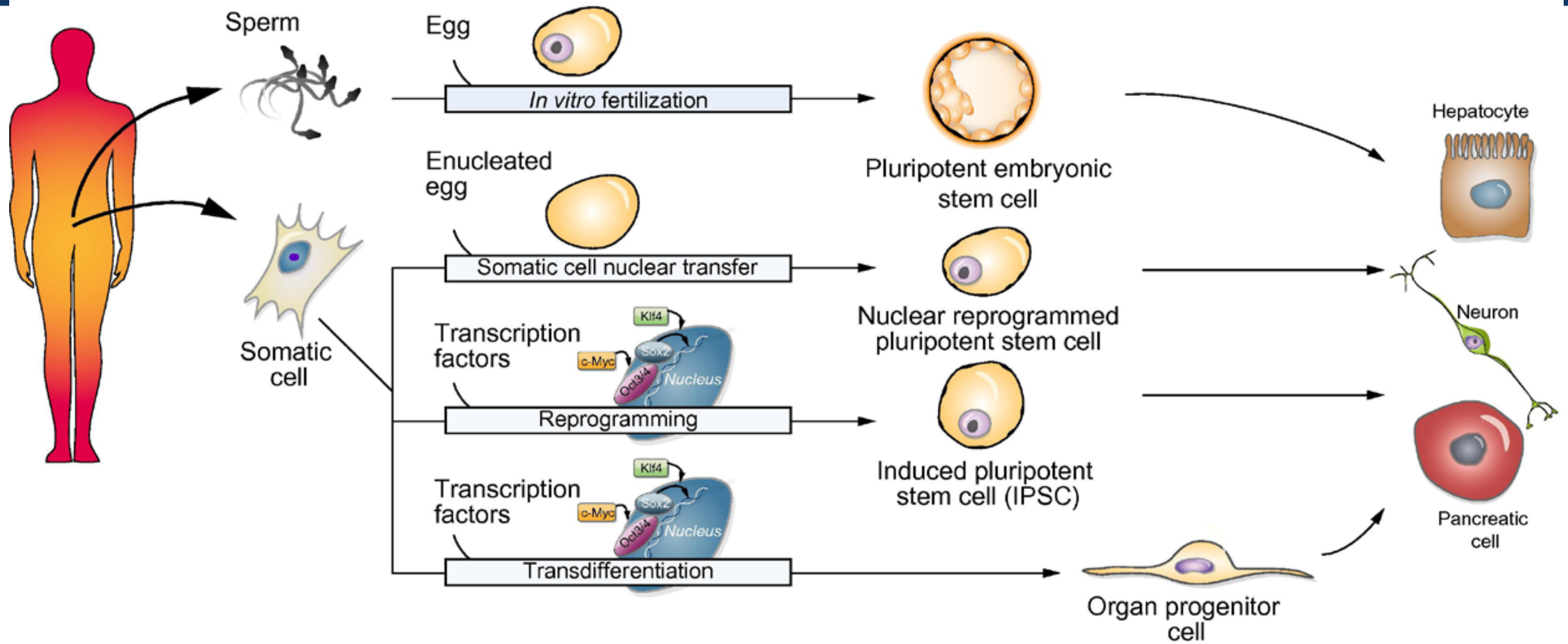

Fig. 1 Derivation of pluripotent stem cells. Pluripotent stem cells, possessing the ability to form any cell type of the human body, can be created using in vitro fertilisation (Steptoe and Edwards), somatic cell nuclear transfer (Gurdon), and transcri...

S. Tamir Rashid , Graeme J.M. Alexander

Induced pluripotent stem cells: From Nobel Prizes to clinical applications

Journal of Hepatology, Volume 58, Issue 3, 2013, 625 - 629

http://dx.doi.org/10.1016/j.jhep.2012.10.026

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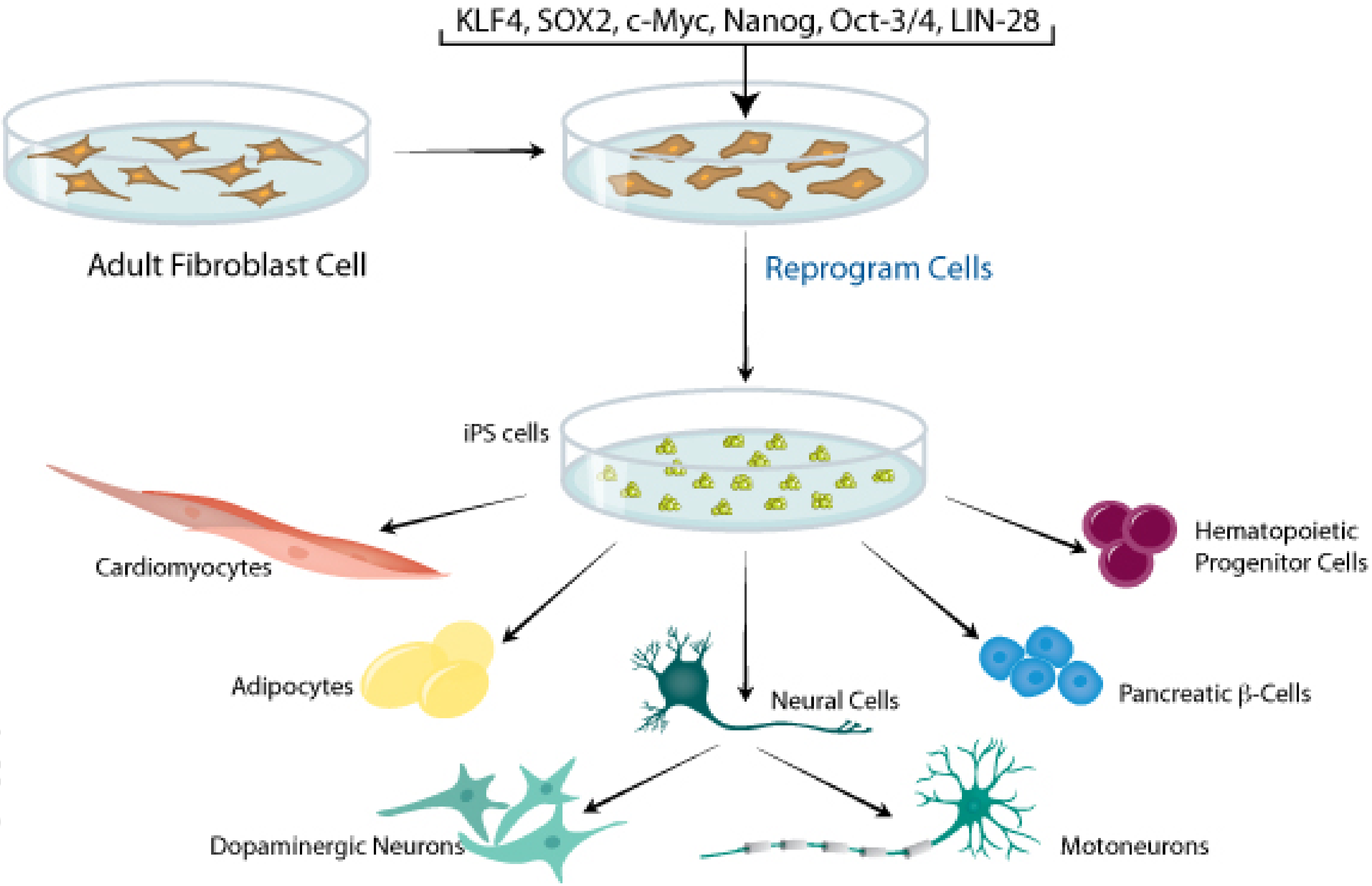
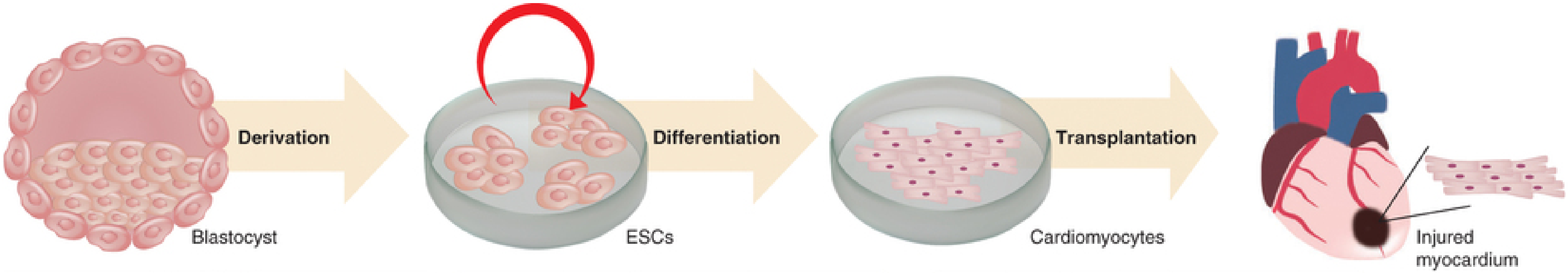


Key Points

- Shinya Yamanaka and Sir John Gurdon were recently awarded the nobel prize for their work on induced pluripotent stem cells (iPSCs)
- iPSCs have the capacity to generate unlimited quantities of any cell type in the human body
- Since their discovery five years ago, numerous studies suggest this new technology could soon be used to generate novel, patient specific *in vitro* disease models and transplantation products
- One of the first disease areas to benefit from this exciting new resource is likely to be Hepatology
- To realize this clinical promise, several key challenges surrounding the reproducibility and epigenetic/genetic stability of the products will first need to be addressed



ESC derivation

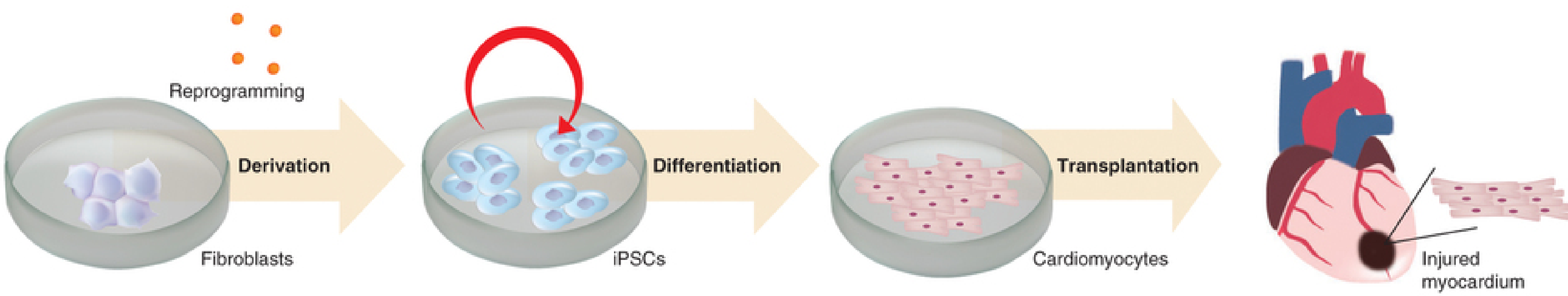
- Oncogenicity of endogenous pluripotency gene expression networks

Differentiation and culture

- Selection for tumorigenic cell clones
- Culture adaptation
- Copy number variations
- Megascale duplications and deletions
- Checkpoint-apoptosis uncoupling
- Incomplete differentiation to terminally differentiated cell types

Transplantation and engraftment

- Contamination of therapeutic cells with residual undifferentiated cells
- Transplantation of non–terminally differentiated tumorigenic cells
- Incomplete silencing of pluripotency networks after differentiation



iPSC derivation

- Pre-existing somatic mutations
- Induction of oncogenic networks related to pluripotency
- Genomic insertion of transgenes
- Induction of genomic aberrations during reprogramming, including chromosomal translocations and subchromosomal lesions
- Rapid demethylation associated with reprogramming, causing genomic instability

Differentiation and culture

- Selection for tumorigenic cell clones
- Culture adaptation
- Copy number variations
- Megascale duplications and deletions
- Checkpoint-apoptosis uncoupling
- Incomplete differentiation to terminally differentiated cell types
- Aberrant methylation causing reactivation of pluripotency transcription factors

Transplantation and engraftment

- Contamination of therapeutic cells with residual undifferentiated cells
- Transplantation of non–terminally differentiated tumorigenic cells
- Incomplete silencing of pluripotency networks after differentiation
- Reactivation of pluripotency transgenes in transplanted cell grafts

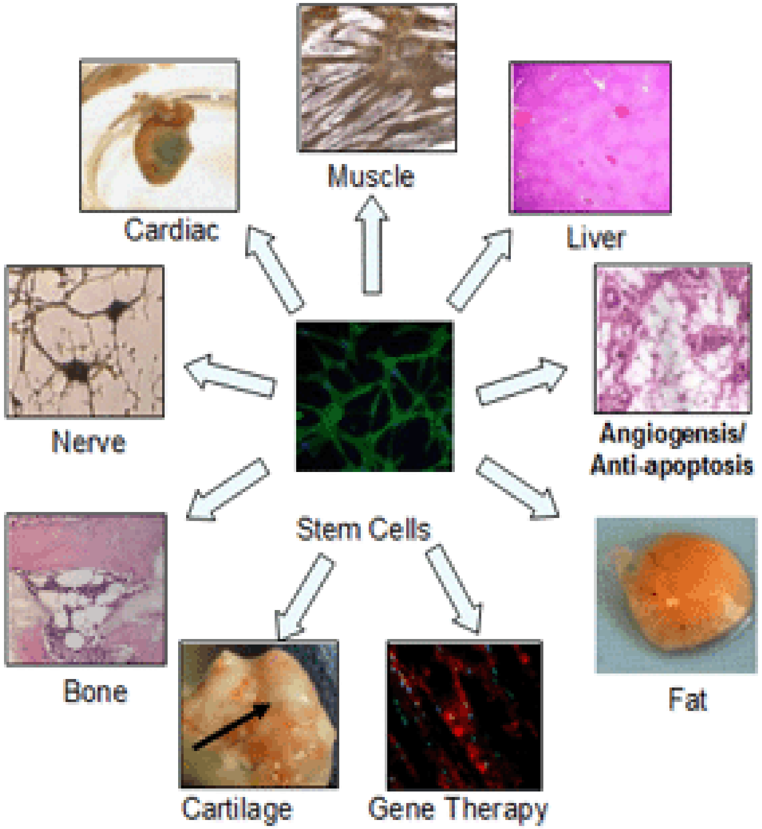
La terapia cellulare come nuova strategia terapeutica

trapianto di cellule per la rigenerazione di un tessuto

* Capacità di **colonizzare** il tessuto ospite

* Capacità di **sopravvivere** nel tessuto ospite

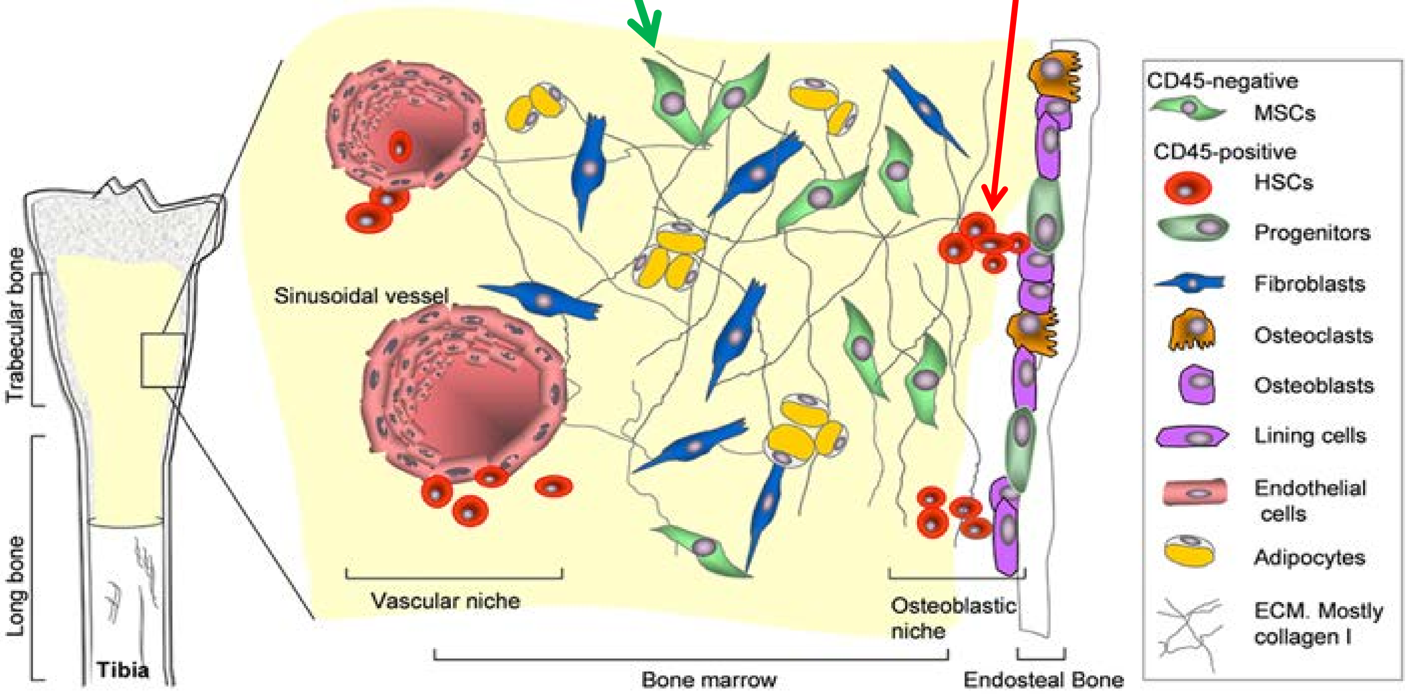
* Capacità di **differenziamento in senso tessuto-specifico**



CELLULE MESENCHIMALI STROMALI /STAMINALI ADULTE (MSC)

MSC

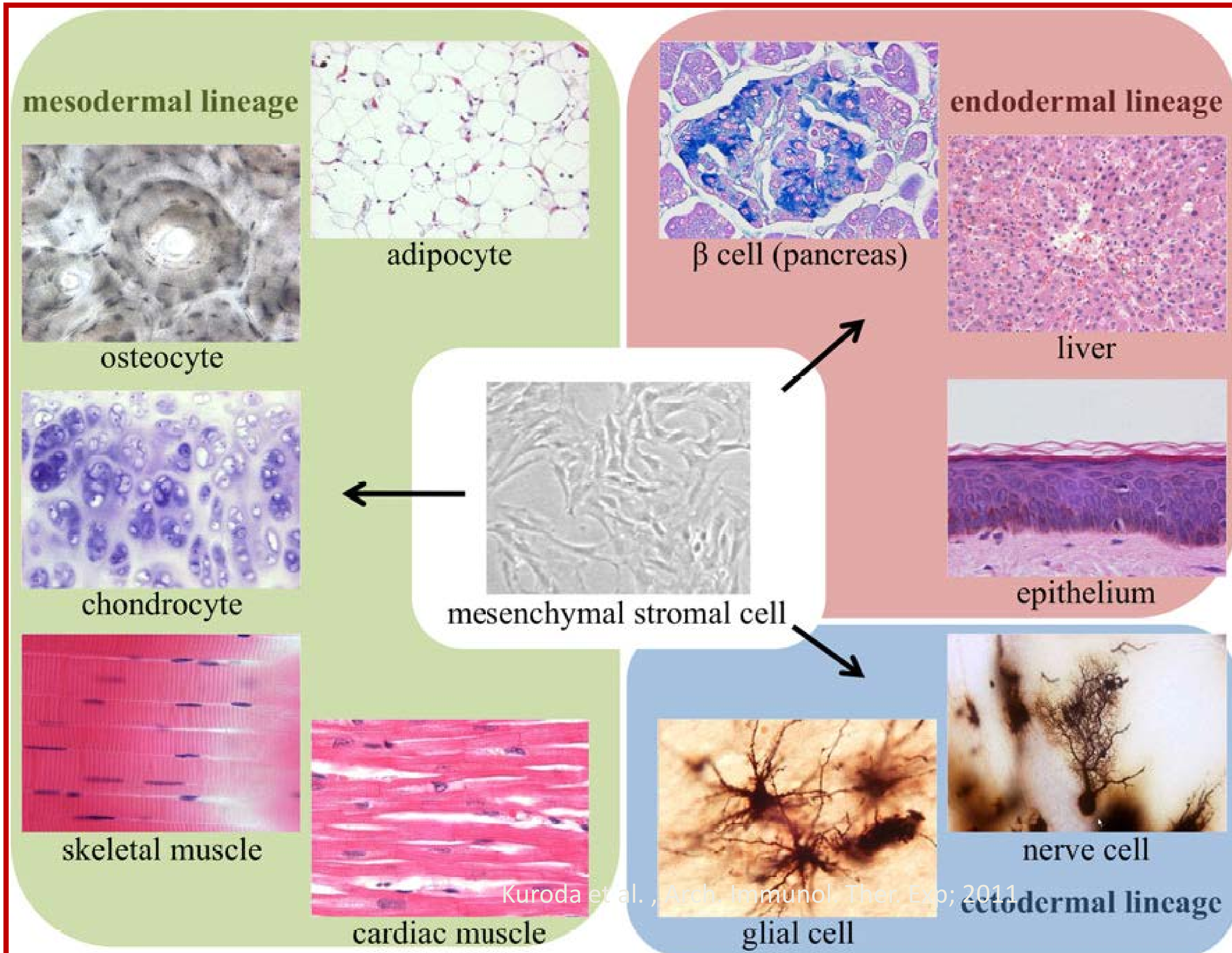
Cellule ematopoietiche Staminali (HSCs)



Grassel & Ahmed, *Frontiers in Bioscience* ; 2007

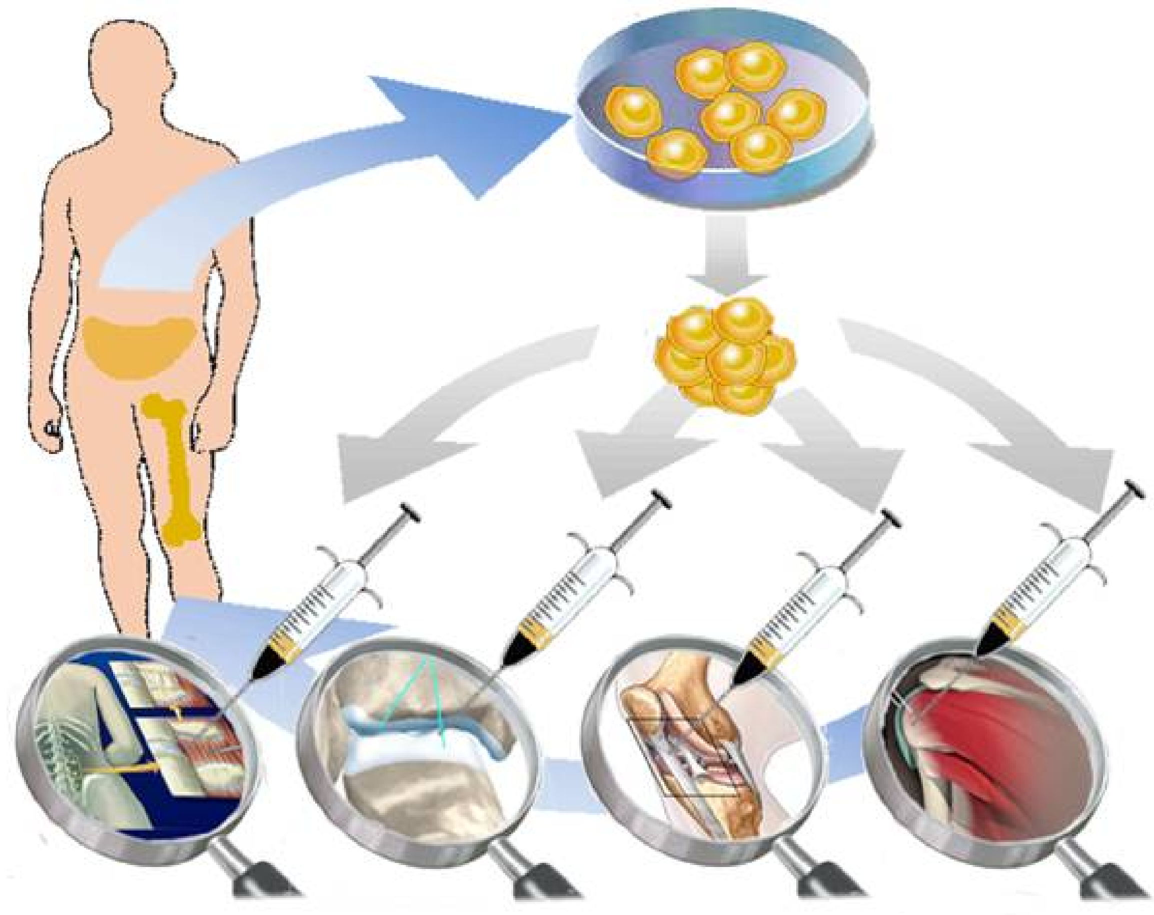
CELLULE MESENCHIMALI STROMALI (MSC) ADULTE

Cellule staminali pluripotenti

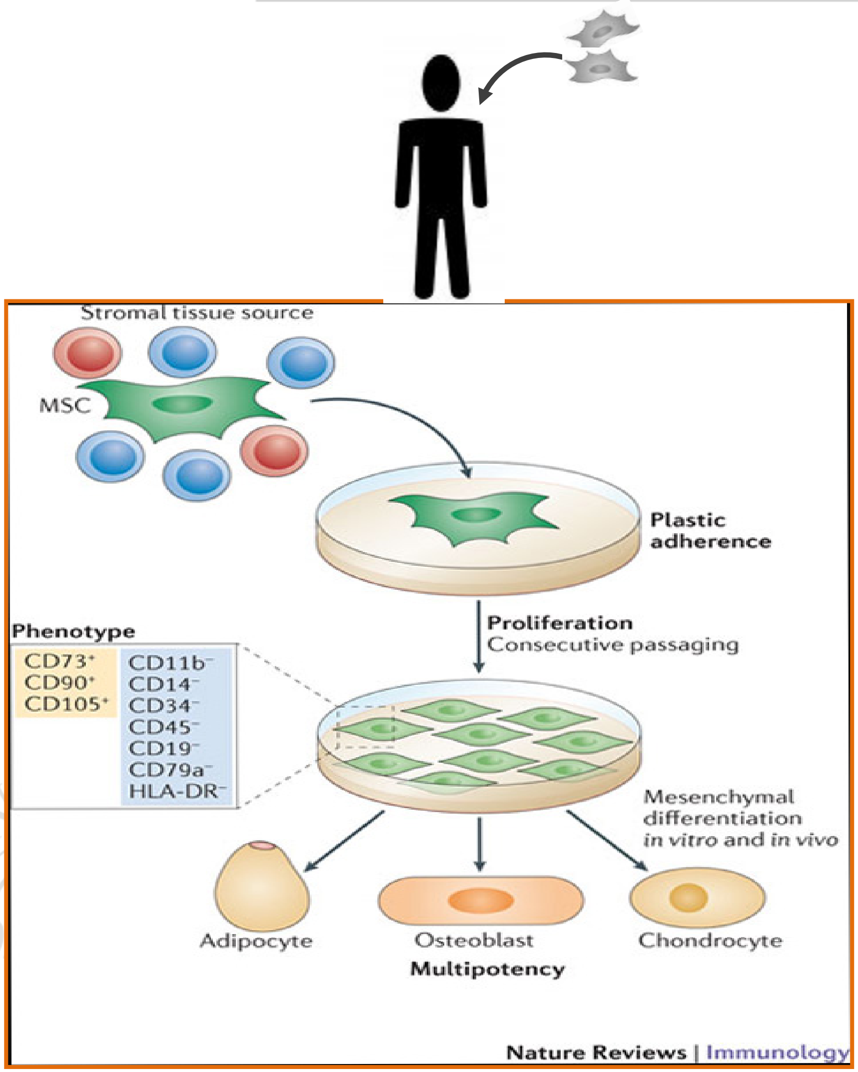


Kuroda et al. , Arch. Immunol. Ther. Exp; 2011

TERAPIA CELLULARE CON CELLULE MESENCHIMALI STROMALI (MSC) ADULTE ISOLATE DA MIDOLLO OSSEO

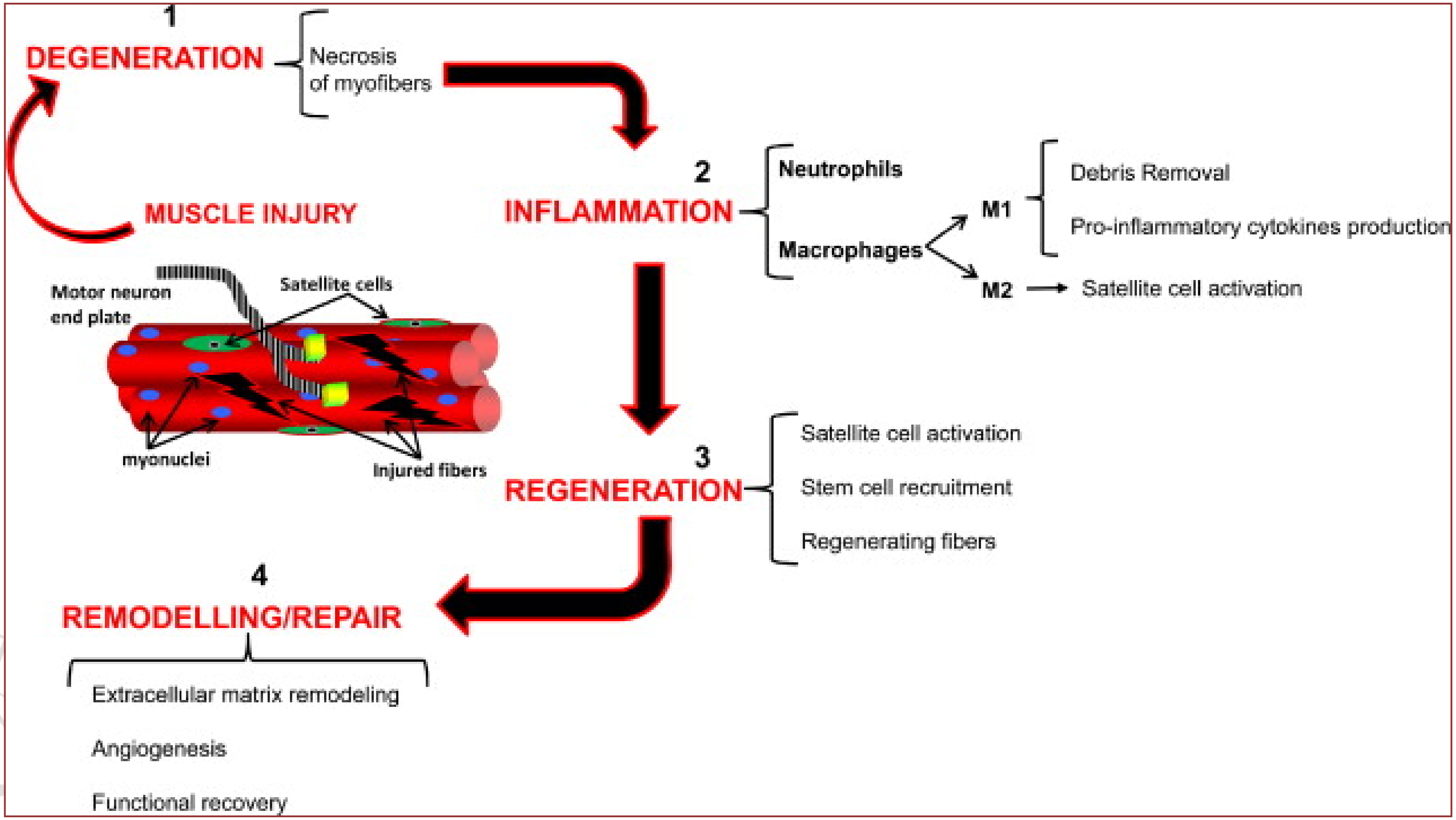


MSC ADULTE e TERAPIA CELLULARE



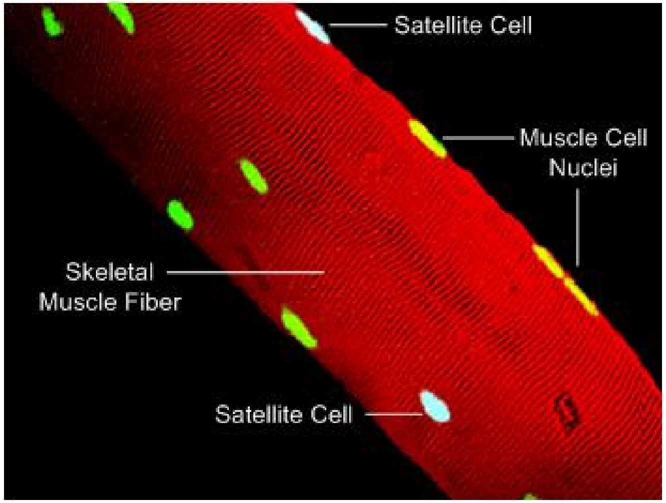
- ✓ Facili da isolare e da espandere *in vitro*
- ✓ Grande plasticità
- ✓ Migrazione verso i siti di lesione
- ✓ Proprietà immunomodulanti ed anti-infiammatorie
- ✓ Non sono immunogeniche
- ✓ Trapianto autologo e eterologo
- ✓ Non hanno potenzialità tumorigeniche
- ✓ Non sollevano questioni di carattere etic

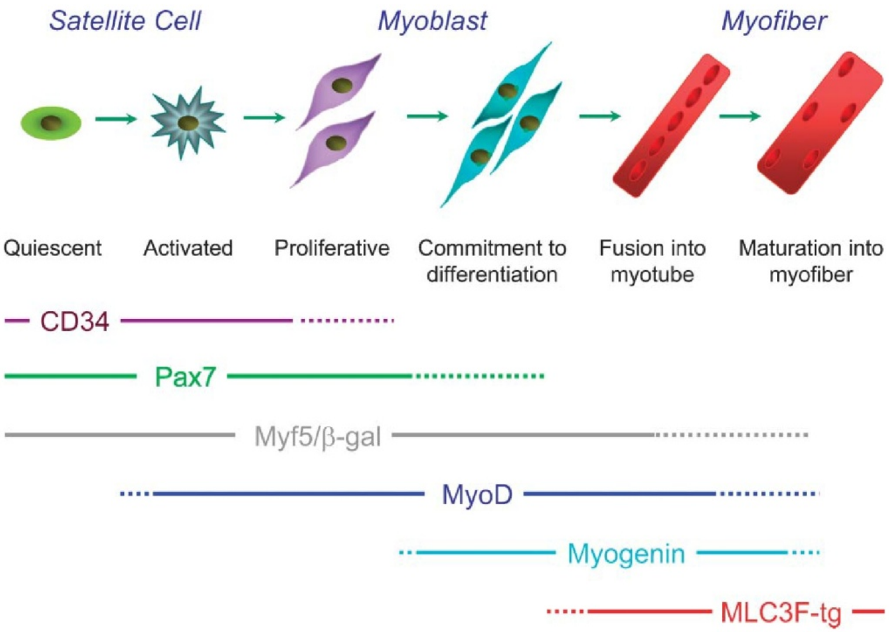
Dalla lesione alla riparazione del tessuto muscolare



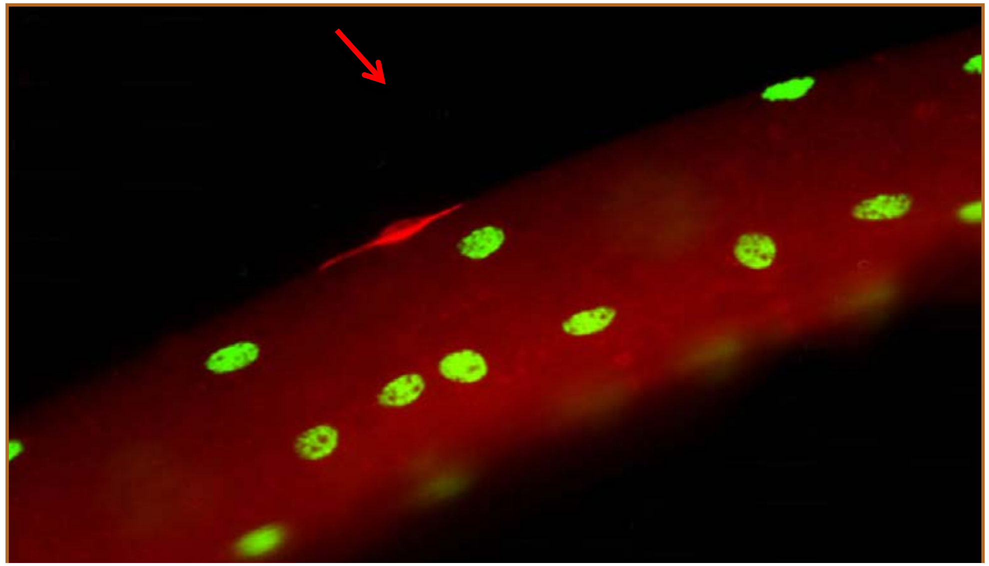
Carosio et al., 2011, Ageing Res Rev.

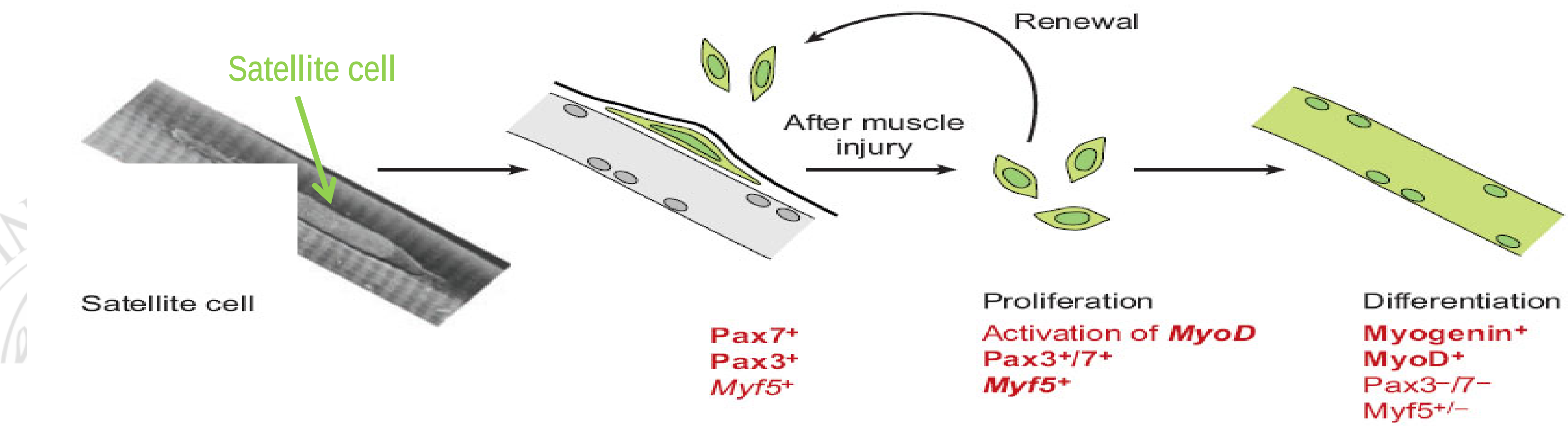
Satellite cells and skeletal muscle regeneration





CELLULE SATELLITI

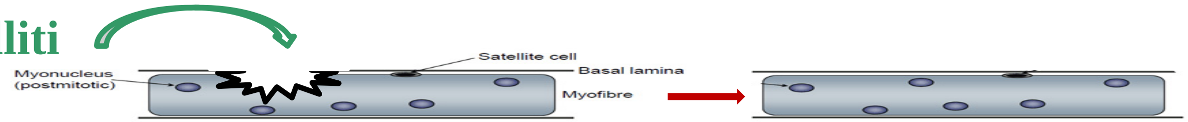




Modificato da Buckingham and Relaix, Annu. Rev. Cell Dev. Biol. , 2007

CELLULE SATELLITI e RIGENERAZIONE MUSCOLARE

Cellule satelliti



Fibra muscolare danneggiata

Riparazione/rigenerazione

Potenzialità terapeutiche

Partridge TA, Morgan JE, Coulton GR, Hoffman EP, Kunkel LM.
Conversion of mdx myofibres from dystrophin-negative to -positive by injection of normal myoblasts.
Nature. 1989; 337:176–179

Cossu G, Sampaolesi M.
New therapies for muscular dystrophy: Cautious optimism.
Trends Mol. Med. 2004; 10: 516-520

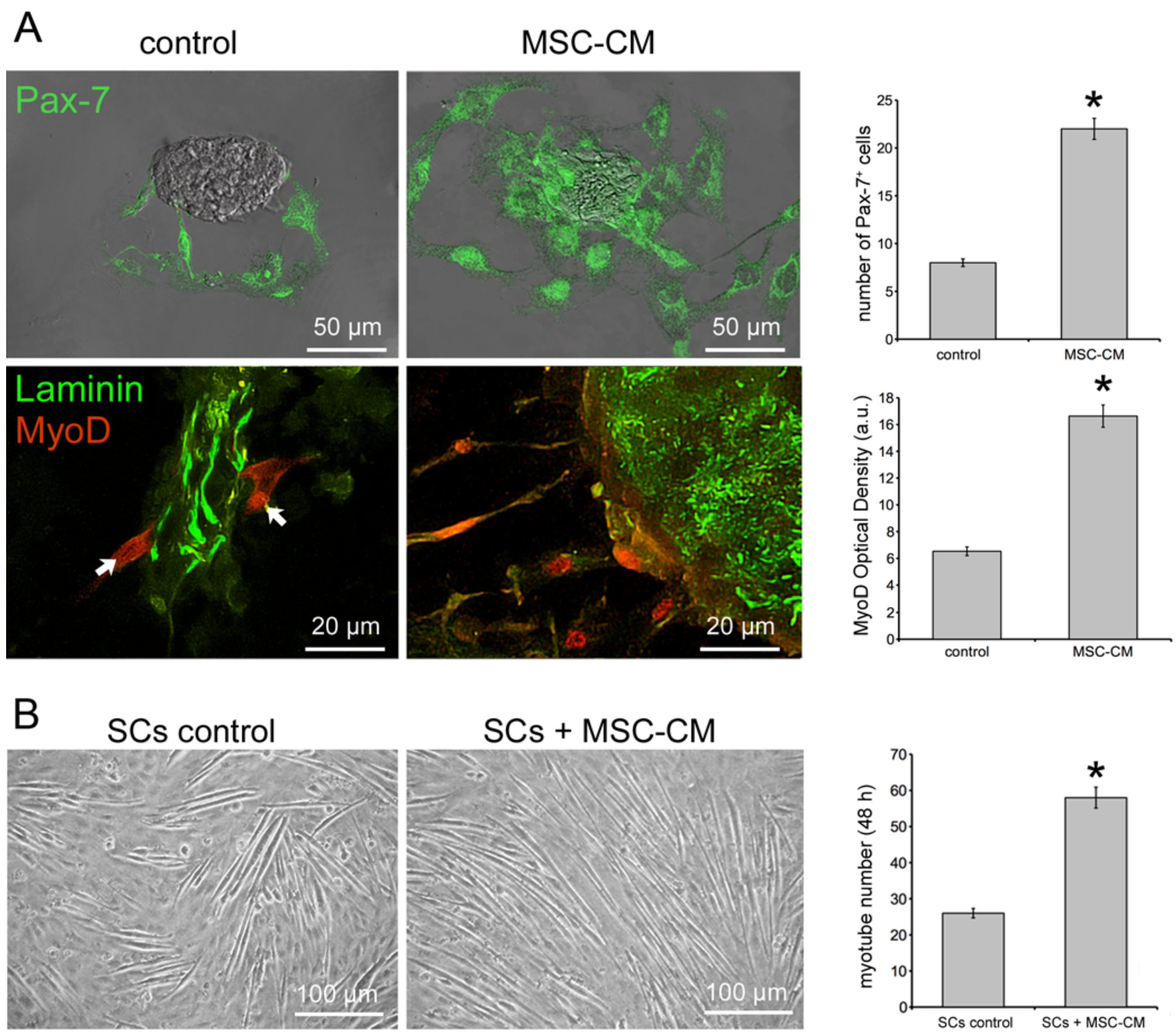
Kuang S, Rudnicki MA.
The emerging biology of satellite cells and their therapeutic potential
Trends Mol Med. 2008; 14: 82-91.

Tedesco, Dellavalle,Diaz-Manera,Messina, Cossu.
Repairing skeletal muscle: regenerative potential of skeletal muscle stem cells.
J. Clin. Invest. 2010, 120: 11-19.

Li Q, Bai Y, Xu Y, Yu H.
Autografting satellite cells to repair damaged muscle induced by repeated compression: an animal model.
Foot Ankle Int. 2010; 31:706-711.

Limiti

- ✓ alta eterogeneità
- ✓ perdita del loro potenziale miogenico dopo l'isolamento e l'espansione in coltura
- ✓ pre-determinazione dipendente dal tipo fibra muscolare da cui derivano
- ✓ scarsa sopravvivenza nel tessuto ricevente
- ✓ incapacità di attraversare la parete dei vasi sanguigni
- ✓ limitata capacità di migrazione intramuscolare


A
control
MSC-CM
Pax-7
50 µm
50 µm
number of Pax-7⁺ cells
25
20
15
10
5
0
control
MSC-CM
*
Laminin
MyoD
20 µm
20 µm
MyoD Optical Density (a.u.)
18
16
14
12
10
8
6
4
2
0
control
MSC-CM
*
B
SCs control
SCs + MSC-CM
100 µm
100 µm
myotube number (48 h)
70
60
50
40
30
20
10
0
SCs control
SCs + MSC-CM
*

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Cellular mechanisms and local progenitor activation to regulate skeletal muscle mass

Marco Cassano, Maurilio Sampaolesi et al.

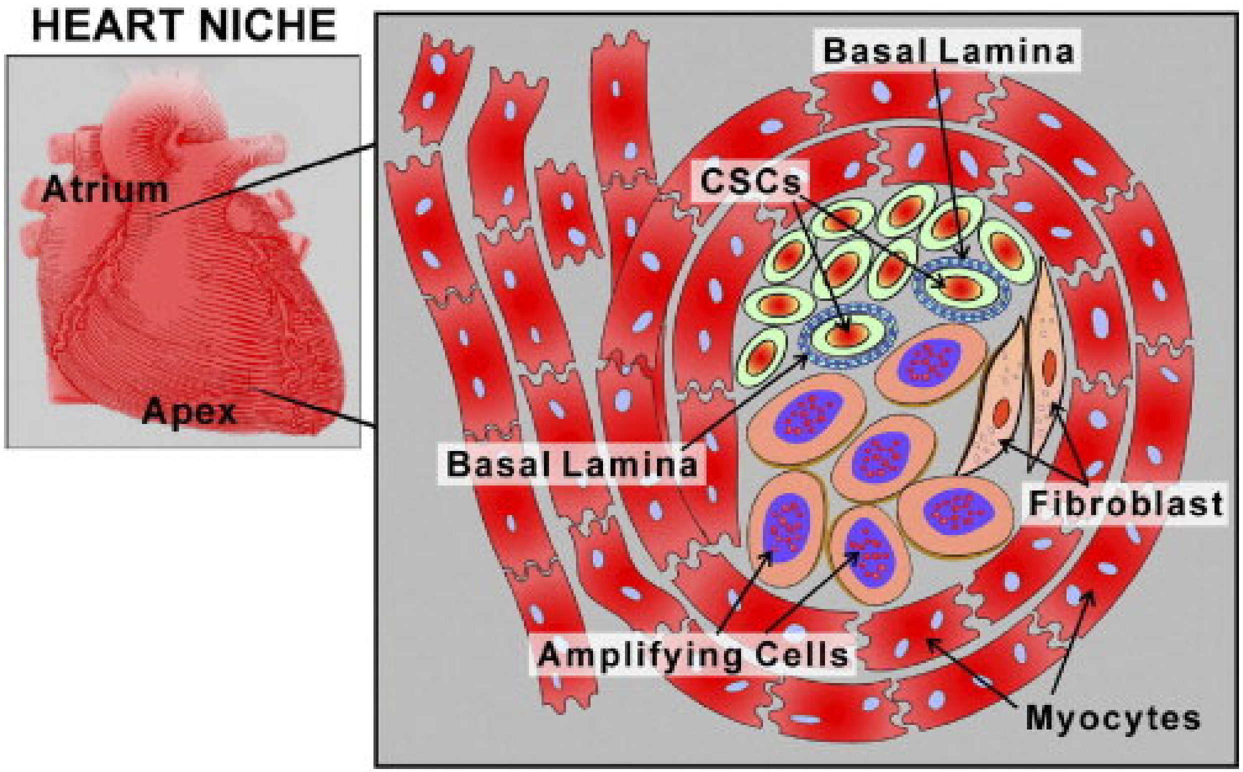
Journal of Muscle Research and Cell Motility

………………………..

To date, there is no accepted treatment to improve muscle size and strength, and these conditions pose a considerable anxiety to patients as well as to public health. …………………..

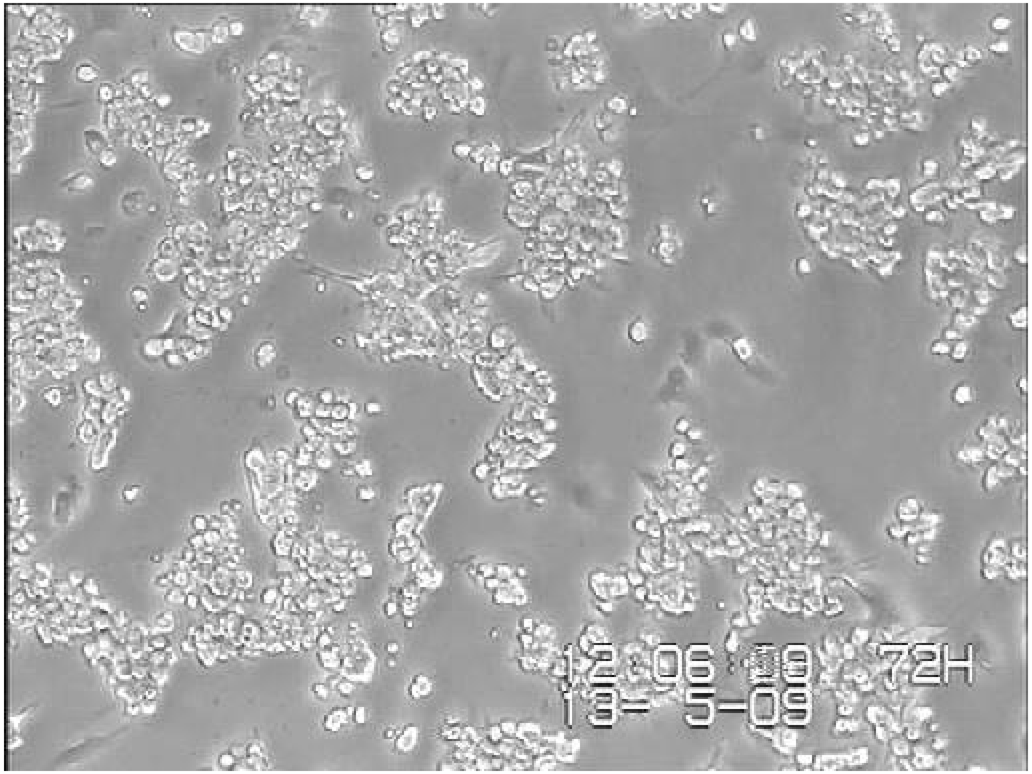
RESIDENT CARDIAC STEM CELLS (CSCS)

Cardiogenic niche

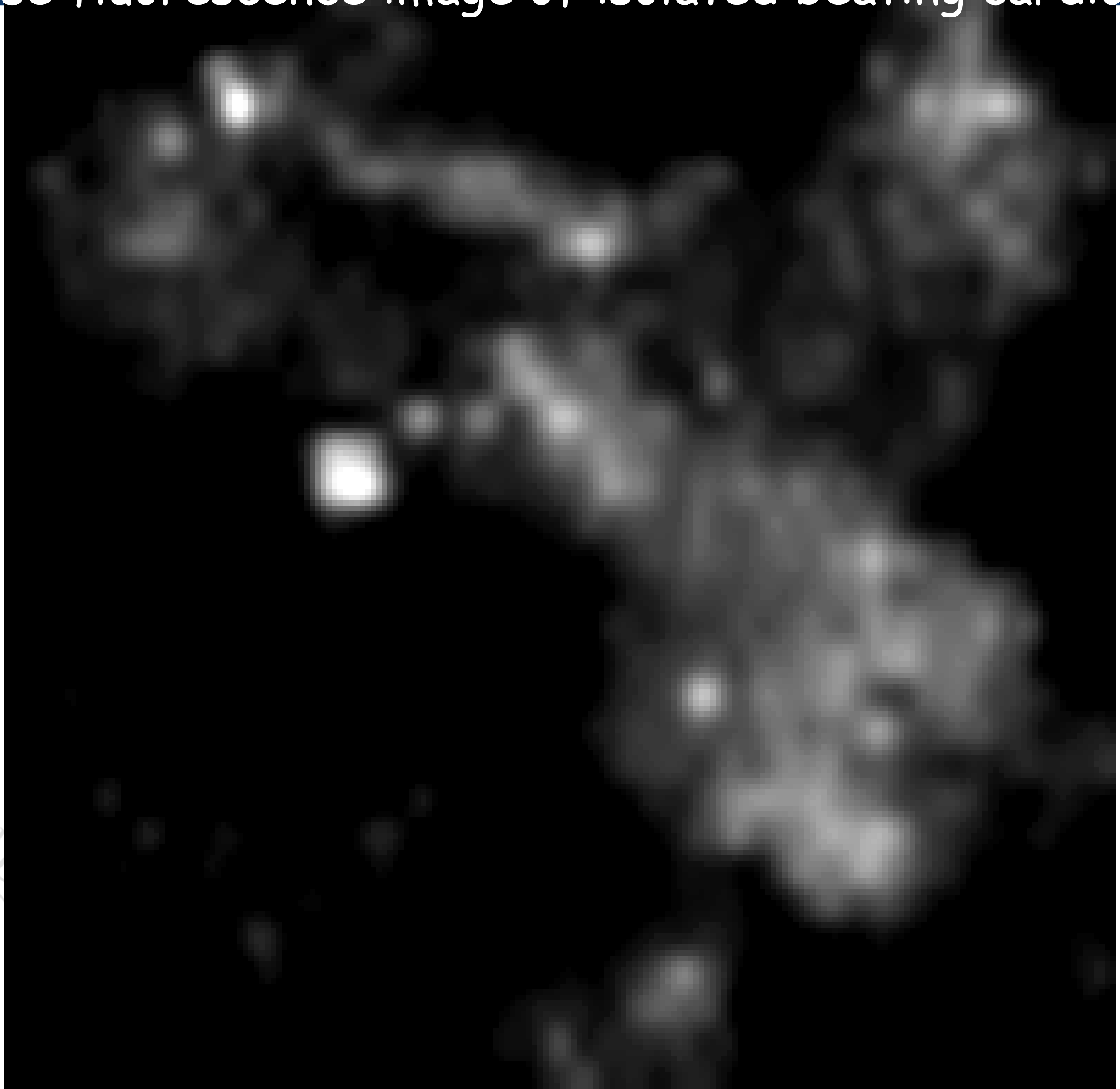


Modificato da Leri et al. 2008; Current Problems in Cardiology

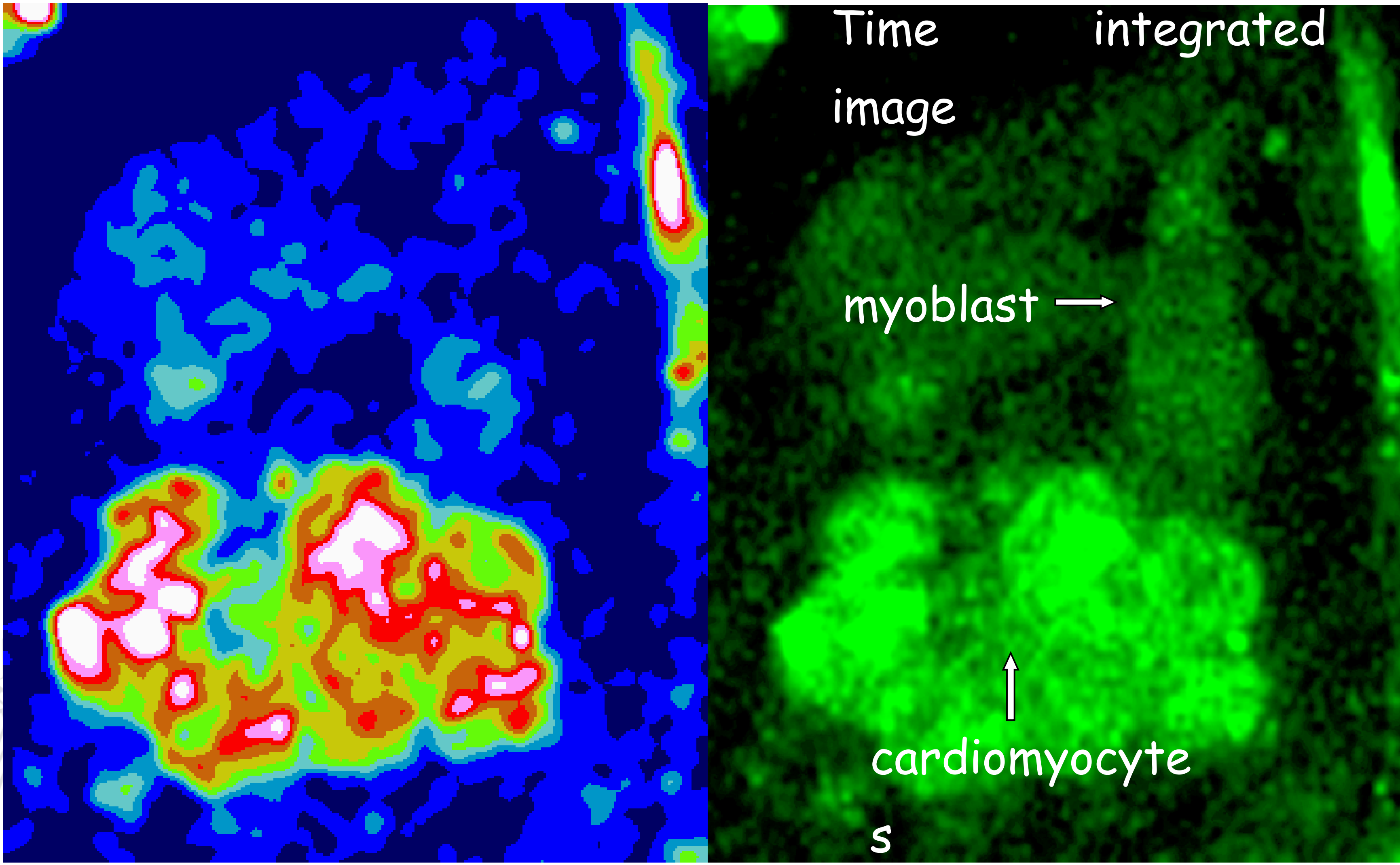
Time-lapse video microscopy of mouse neonatal cardiac cells



Time-course fluorescence image of isolated beating cardiomyocytes

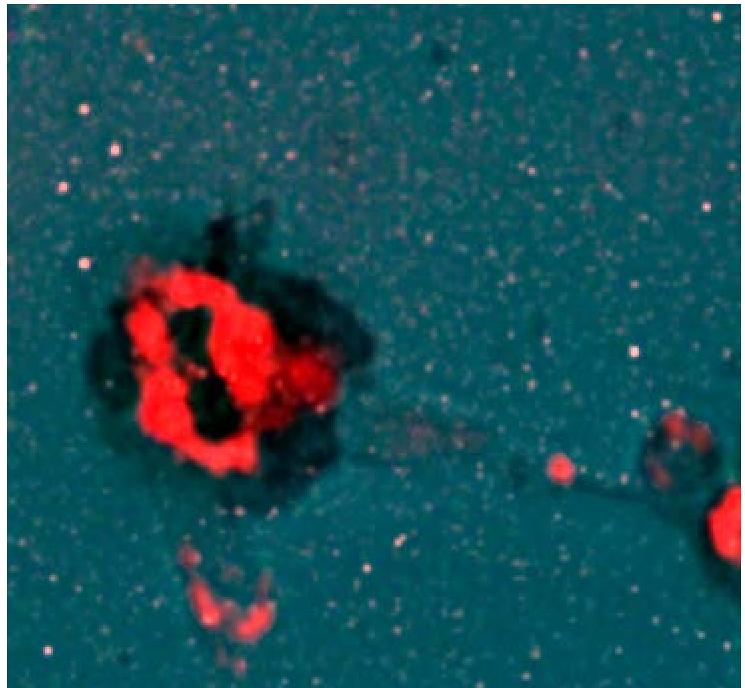


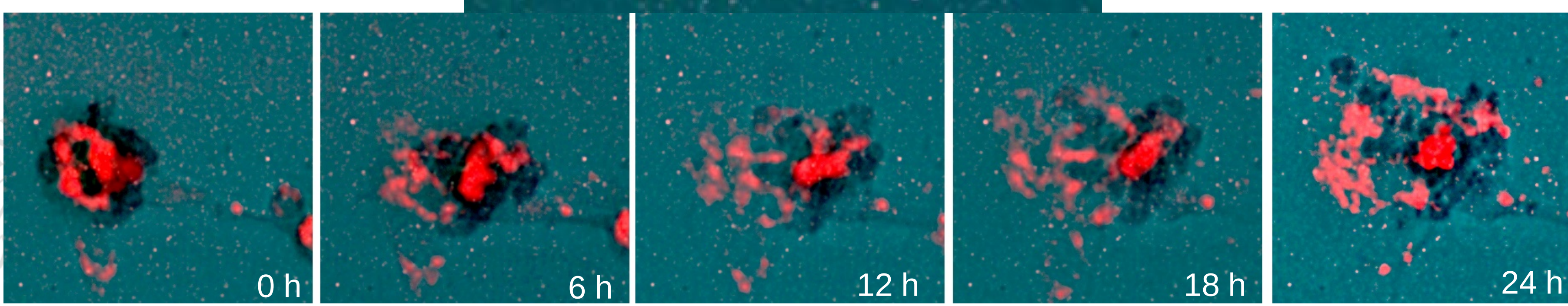
Co-culture of C2C12 cells and beating cardiomyocytes: evidence for Ca^{2+} transient propagation between the two cell types



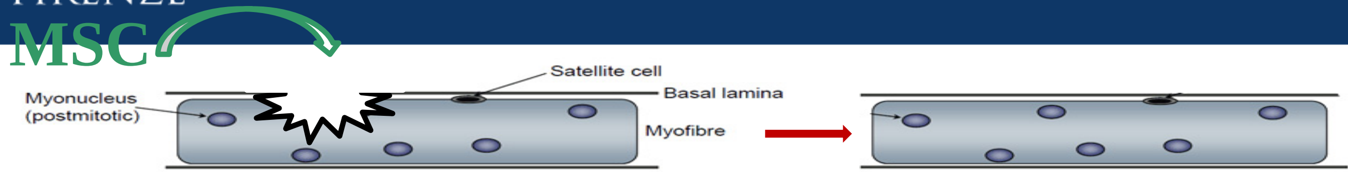
TIME LAPSE FLUORESCENCE VIDEOMICROSCOPY

CO-CULTURE NEONATAL CARDIOMYOCITE -MSC-*DIL*





CONTRIBUTO DELLE MSC ALLA RIPARAZIONE/REGENERAZIONE DEL MUSCOLO SCHELETRICO



Fibra muscolare danneggiata **Riparazione/rigenerazione**

Cell Transplant. 2011;20(2):217-31. doi: 10.3727/096368910X522117. Epub 2010 Aug 18.

Long-term contribution of human bone marrow mesenchymal stromal cells to skeletal muscle regeneration in mice.

de la Garza-Rodea AS, van der Velde I, Boersma H, Gonçalves MA, van Bekkum DW, de Vries AA, Knaän-Shanzer S.

Virus and Stem Cell Biology Laboratory, Department of Molecular Cell Biology, Leiden University Medical Center, Leiden, The Netherlands.

Tissue Eng. 2004 Jul-Aug;10(7-8):1093-112.

Allogeneic bone marrow-derived mesenchymal stromal cells promote the regeneration of injured skeletal muscle without differentiation into myofibers.

Natsu K, Ochi M, Mochizuki Y, Hachisuka H, Yanada S, Y

Department of Orthopaedic Surgery, Programs for Applied Biom
Hiroshima University, Hiroshima 734-8551, Japan. natchi@hiros

original article © The American Society of Gene & Cell Therapy

Long-term Engraftment of Multipotent Mesenchymal Stromal Cells That Differentiate to Form Myogenic Cells in Dogs With Duchenne Muscular Dystrophy

Yuko Nitahara-Kasahara[1], Hiromi Hayashita-Kinoh[1], Sachiko Ohshima-Hosoyama[1], Hironori Okada[1], Michiko Wada-Maeda[1], Akinori Nakamura[1], Takashi Okada[1] and Shin'ichi Takeda[1]

J Tissue Eng Regen Med. 2012 Dec;6 Suppl 3:s60-7.

Immediate and delayed transplantation of mesenchymal stem cells improve muscle force after skeletal muscle injury in rats.

Winkler T, von Roth P, Radojewski P, Urbanski A, Hahn S, Preininger B, D

Center for Musculoskeletal Surgery and Julius Wolff Institute, Berlin Brandenburg C
Berlin, Berlin, Germany.

Gender Medicine/Vol. 9, No. 2, 2012

Mesenchymal Stem Cell Therapy Following Muscle Trauma Leads to Improved Muscular Regeneration in Both Male and Female Rats

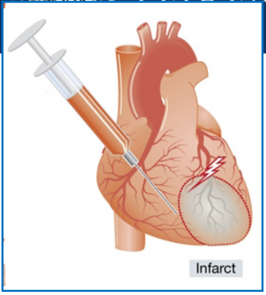
Philipp von Roth, MD[1,2,3], Georg N. Duda, PhD[1,2,3], Piotr Radojewski, Bernd Preininger, MD, Carsten Perka, MD[1,2], and Tobias Winkler, MD, PhD[2]
...medizin Berlin, Free University of Berlin and ...-Brandenburg Center for Regenerative Therapies, ...egenerative Therapies, Berlin, Germany

Cytotherapy. 2008;10(3):254-64. doi: 10.1080/14653240802020381.

Dynamic distribution of bone marrow-derived mesenchymal stromal cells and change of pathology after infusing into mdx mice.

Feng SW, Lu XL, Liu ZS, Zhang YN, Liu TY, Li JL, Yu MJ, Zeng Y, Zhang C.

CONTRIBUTO DELLE MSC ALLA RIPARAZIONE/REGENERAZIONE CARDIACA

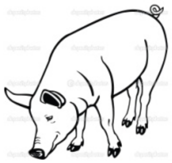


PNAS

Cardiac repair with intramyocardial injection of allogeneic mesenchymal stem cells after myocardial infarction

Luciano C. Amado*†, Anastasios P. Saliaris*†, Karl H. Schuleri*†, Marcus St. John*, Jin-Sheng Xie*, Stephen Cattaneo‡, Daniel J. Durand*†, Torin Fitton‡, Jin Qiang Kuang§¶, Garrick Stewart*, Stephanie Lehrke*†, William W. Baumgartner‡, Bradley J. Martin§¶, Alan W. Heldman*†, and Joshua M. Hare*†‖

*Department of Medicine, Cardiology Division, and ‡Department of Surgery, Division of Cardiac Surgery, The Johns Hopkins Hospital, Blalock 618, 600 North ... Johns Hopkins



Cardiovascular Research (2008) 77, 515–524
doi: 10.1093/cvr/cvm046

Direct intramyocardial injection of mesenchymal stem cell sheet fragments improves cardiac functions after infarction

Chung-Chi Wang[1†], Chun-Hung Chen[2†], Wei-Wen Lin[3], ...
Po-Hong Lai[2], Yi-Chun Yeh[2], Yen Chang[1*], and Hsing-...

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association.

Allogeneic Mesenchymal Stem Cell Transplantation in Postinfarcted Rat Myocardium : Short- and Long-Term Effects

Wangde Dai, Sharon L. Hale, Bradley J. Martin, Jin-Qiang Kuang, Joan S. Dow, Loren E. Wold and Robert A. Kloner

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 3,
© 2010 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION ISSN 1936-8...
PUBLISHED BY ELSEVIER INC. DOI: 10.1016/j.jcin...

Reparative Effects of Allogeneic Mesenchymal Precursor Cells Delivered Transendocardially in Experimental Nonischemic Cardiomyopathy

Peter J. Psaltis, MD, PHD,*† Angelo Carbone, BSC,* Adam J. Nelson, BMEDSC,* Dennis H. Lau, MD,* Troy Jantzen, PHD,§ Jim Manavis, BSC,‡ Kerry Williams, DIP APPSC,* Silviu Itescu, MD, PHD,‖ Prashanthan Sanders, MD, PHD,* Stan Gronthos, PHD,† Andrew C. W. Zannettino, PHD,† Stephen G. Worthley, MD, PHD*

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Coronary vein infusion of multipotent stromal cells from bone marrow preserves cardiac function in swine ischemic cardiomyopathy via enhanced neovascularization

Takatoshi Sato[1,*], Yoshitaka Iso[2,*], Taro Uyama[3], Keisuke Kawachi[2], Kohei Wakabayashi[2], Yasutoshi Omori[1], Teruko Soda[1], Makoto Shoji[1], Shinji Koba[1], Shin-Ichiro Yokoyama[4], Noboru Fukuda[5], Satoshi Saito[4], Takashi Katagiri[1], Youichi Kobayashi[1], Youichi Takeyama[2], Akihiro Umezawa[3] and Hiroshi Suzuki[2]

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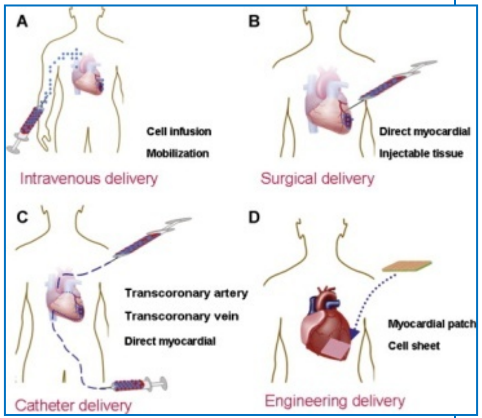

Table I. Clinical trials using BM-MSC therapy for cardiac repair/regeneration

Trial name	*ClinicalTrials.gov Identifier*	*Sponsor/ Collaborator*	*Location*	*Disease*	*Source*	*Route of delivery*	*Patients*	*Status*
Prospective randomized study of mesenchymal stem cell therapy in patients undergoing cardiac surgery (PROMETHEUS)	NCT00587990	National Heart, Lung, and Blood Institute (NHLBI) Johns Hopkins University Specialized Center for Cell Based Therapy	USA	Chronic ischemic left ventricular disfunction	Autologous	Intramyocardial injection	45	Completed
Stem cell injection to treat heart damage during open heart surgery	NCT01557543	National Heart, Lung, and Blood Institute (NHLBI)	USA	Heart disease Ischemic heart disease Coronary artery disease	Autologous	Intramyocardial injection	24	Recruiting
Safety and efficacy of intracoronary adult human mesenchymal stem cells after acute myocardial infarction	NCT01392105	Yonsei University FCB Pharmicell Co Ltd.	Republic of Korea	Acute myocardial infarction (AMI)	Autologous	Intracoronary injection	80	Completed
Stem cell therapy for vasculogenesis in patients with severe myocardial ischemia	NCT00260338	Righospitalet, Copenhagen Denmark Jens Kastrup	Denmark	Myocardial ischemia Coronary heart disease	Autologous	Intramyocardial injection	31	Completed
Autologous mesenchymal stromal cell therapy in heart failure	NCT00644410	Righospitalet, Copenhagen Denmark Jens Kastrup	Denmark	Heart failure	Autologous	Intramyocardial injection	60	Recruiting
Prochymal® (human adult stem cells) intravenous infusion following acute myocardial infarction (AMI)	NCT00877903	Osiris Therapeutics	USA Canada	Acute myocardial infarction (AMI)	Allogenic	Intravenous injection	220	Active, not recruiting
Safety Study of AMI MultiStem® to treat Heart attacks	NCT00677222	Athersys, Inc PPD Angiotech Pharmaceuticals	USA	Acute myocardial infarction (AMI)	Allogenic	Via catheter into peri-vascular space injection	25	Completed
A phase II dose-escalation study to assess the feasibility and safety of transendocardial delivery of three different doses of allogeneic mesenchymal precursor cells (MPCs) in subjects with heart failure	NCT00721045	Angioblast Systems, U.S.	USA	Heart failure	Allogenic	Trans-endocardial injection	60	Unknown (*last verified June 2010: active, not recruiting*)

Riduzione aritmie
Riduzione cicatrice
Attenuazione disfunzione contrattile ventricolare
Aumento frazione di eiezione ventricolare sinistra