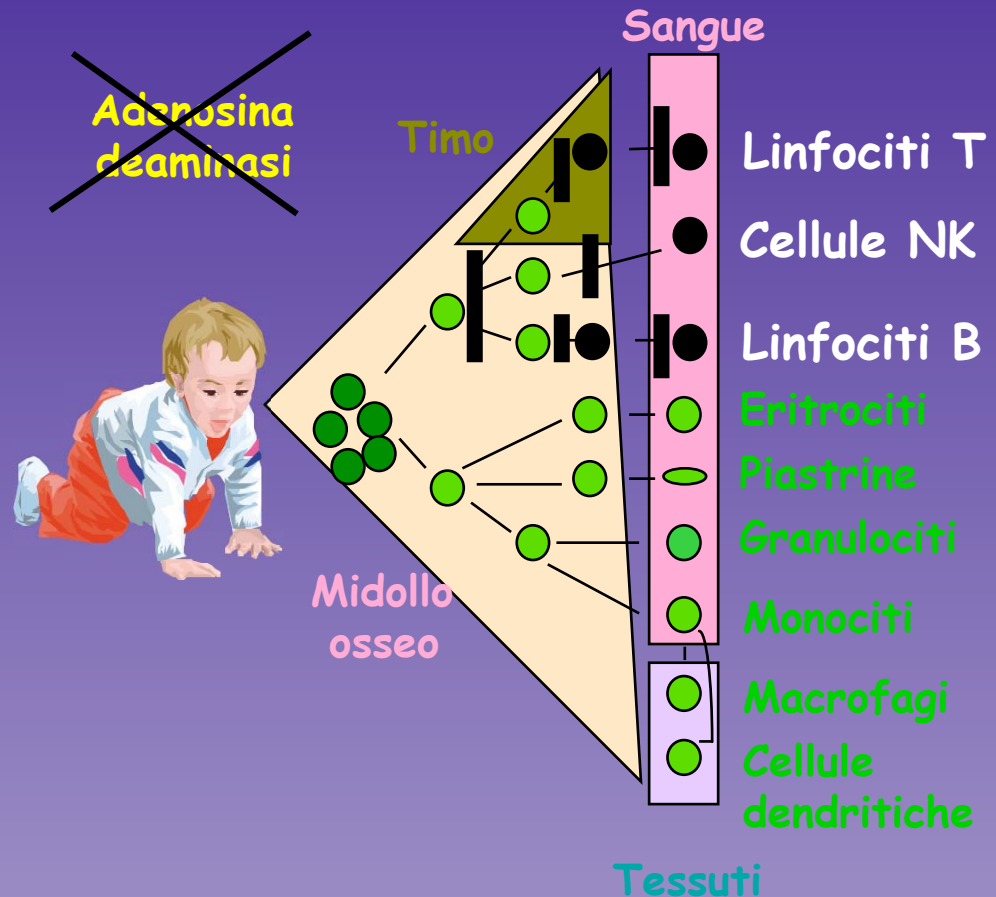


Quando il problema è **semplice**.....: il caso della ricostituzione del sistema immune nell'ADA-SCID:

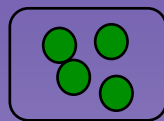
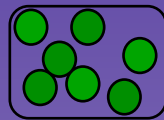
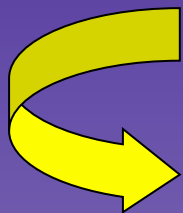
Severe combined immuno defincency

- Alterazioni nel metabolismo delle purine, accumulo intracellulare di dAXP e adenosina
- Difetto nel differenziamento, nella crescita e nelle funzioni dei linfociti
- Assenza di risposta immune umorale e cellulare, infezioni ricorrenti
- Il fenotipo dipende dal tipo di mutazione nel gene ADA

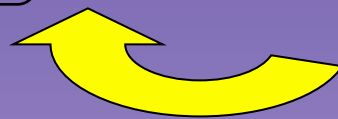


Terapia genica dell' ADA-SCID con cellule staminali

Vettore retrovirale



Cellule staminali
del midollo osseo



Timo

Midollo

Sangue

Tessuti

Linfociti T

Cellule NK

Linfociti B

Eritrociti

Piastrine

Granulociti

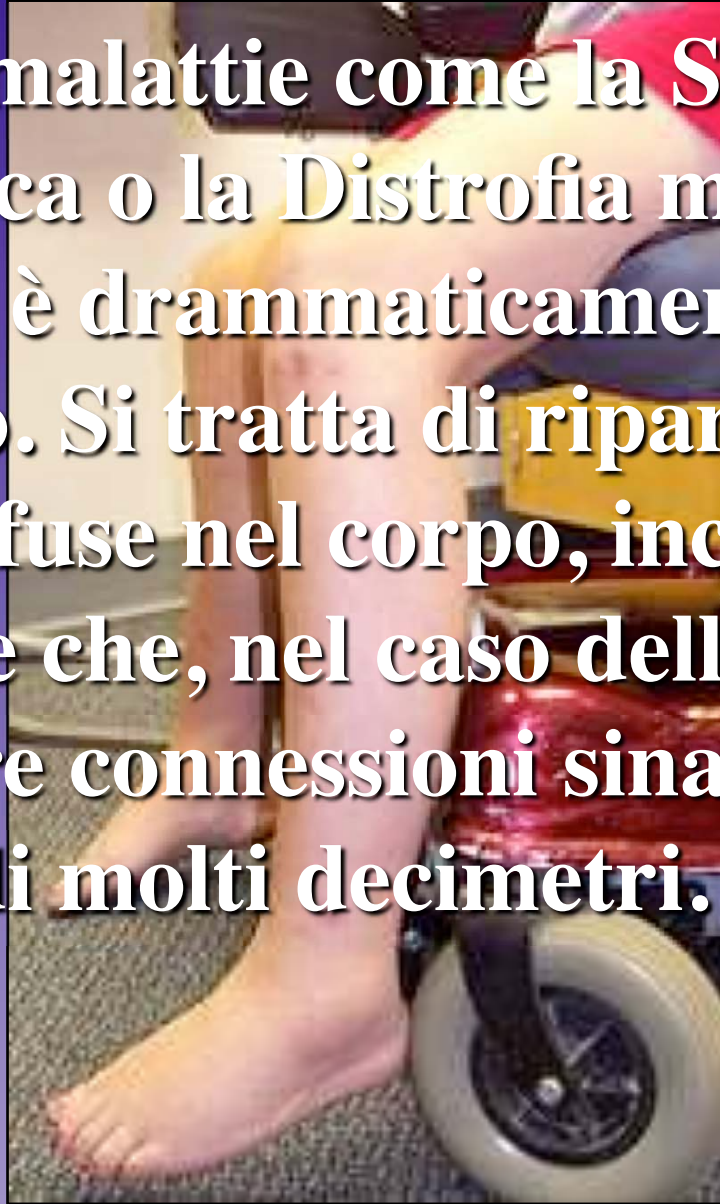
Monociti

Macrofagi

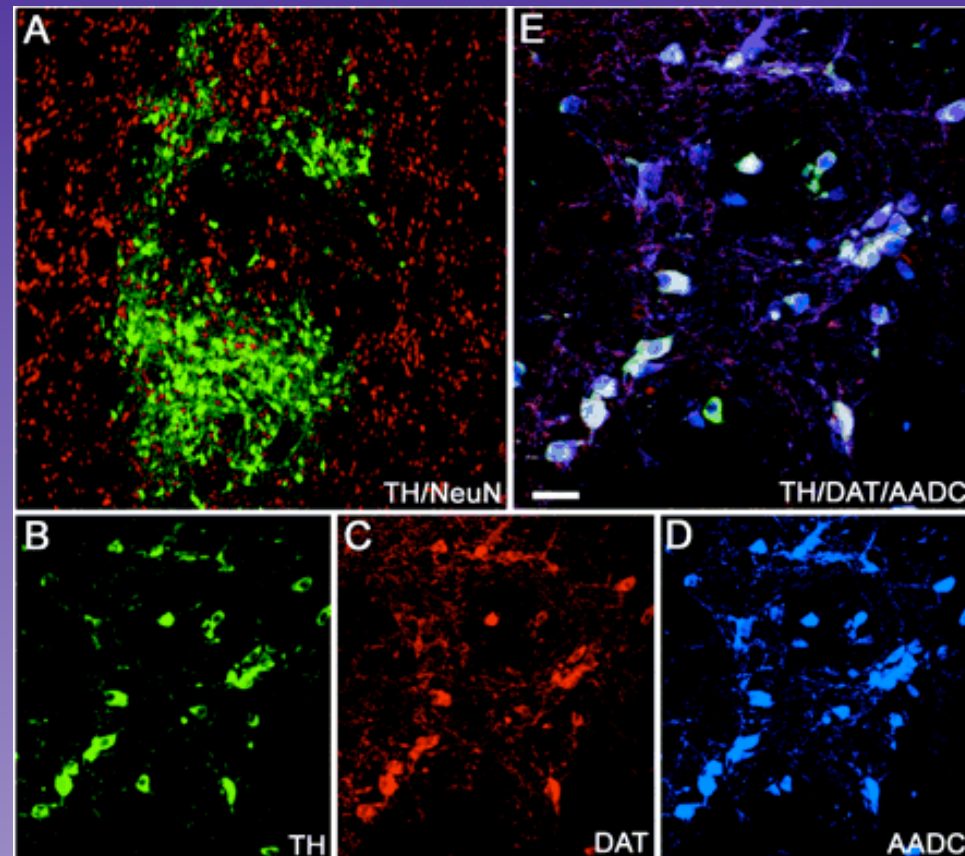
Cellule dendritiche



Per altre malattie come la Sclerosi Laterale Amiotrofica o la Distrofia muscolare il problema è drammaticamente più complesso. Si tratta di riparare tessuti e cellule diffuse nel corpo, incapaci di dividersi e che, nel caso della SLA devono ricostituire connessioni sinaptiche a distanze di molti decimetri.



When injected into the brain of DOPAdeficient rats, neural stem cells restore the presence of dopaminergic neurons



Same effect was observed with embryonic stem cells

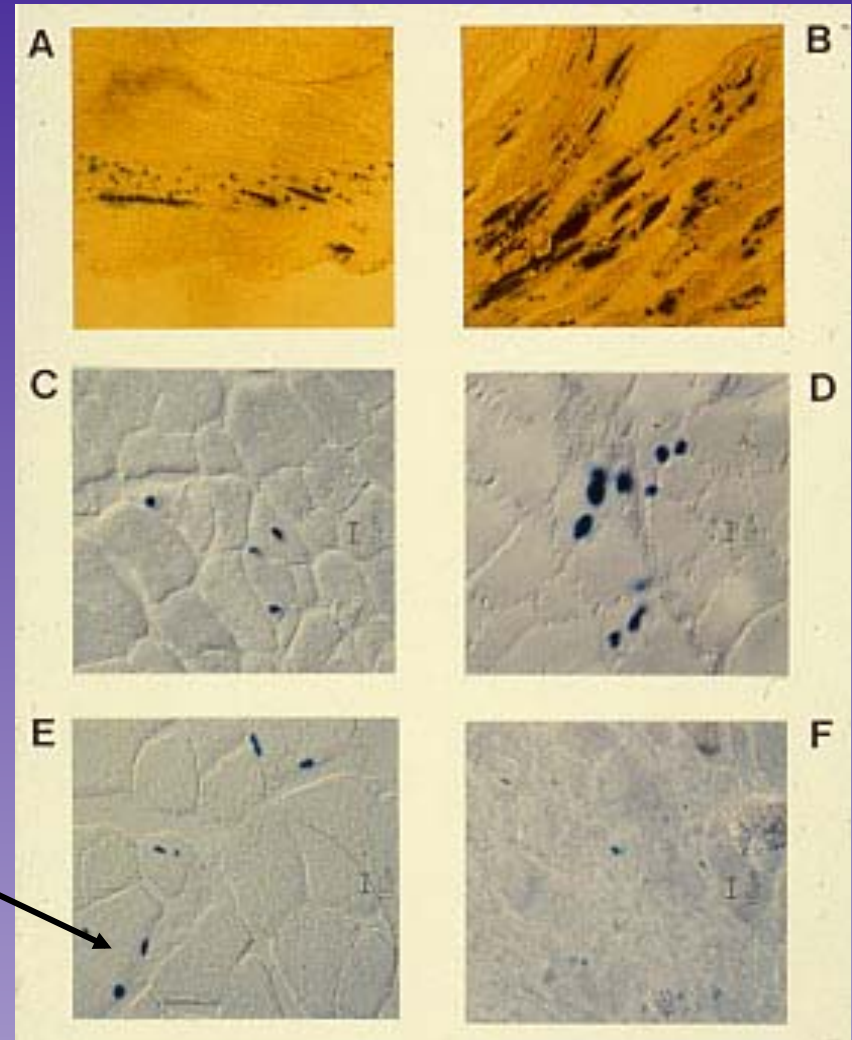
In 1998 we reported that adult mouse bone marrow contains cells that can form skeletal muscle in vivo after BMT



Bone marrow from donor MLC1/3F-nLacZ mice was transplanted into lethally irradiated mice

The MLC1/3F LacZ restricts reporter gene expression to striated muscle.

Blue nuclei (LacZ+) indicate striated muscle differentiation of donor cells



Bone marrow transplantation appeared as a possible therapy for muscular dystrophies

And indeed after one year:

Dystrophin expression in the *mdx* mouse restored by stem cell transplantation

Emanuela Gussoni*, Yuko Soneoka††, Corinne D. Strickland*, Elizabeth A. Buzney*, Mohamed K. Khan§, Alan F. Flint*†, Louis M. Kunkel*†† & Richard C. Mulligan††

* Division of Genetics, † Howard Hughes Medical Institute and
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Massachusetts 02115 USA

†† Department of Genetics, Harvard Medical School, Boston, Massachusetts 02115,
USA

But, in reality only few muscle fibers became Dystrophin +



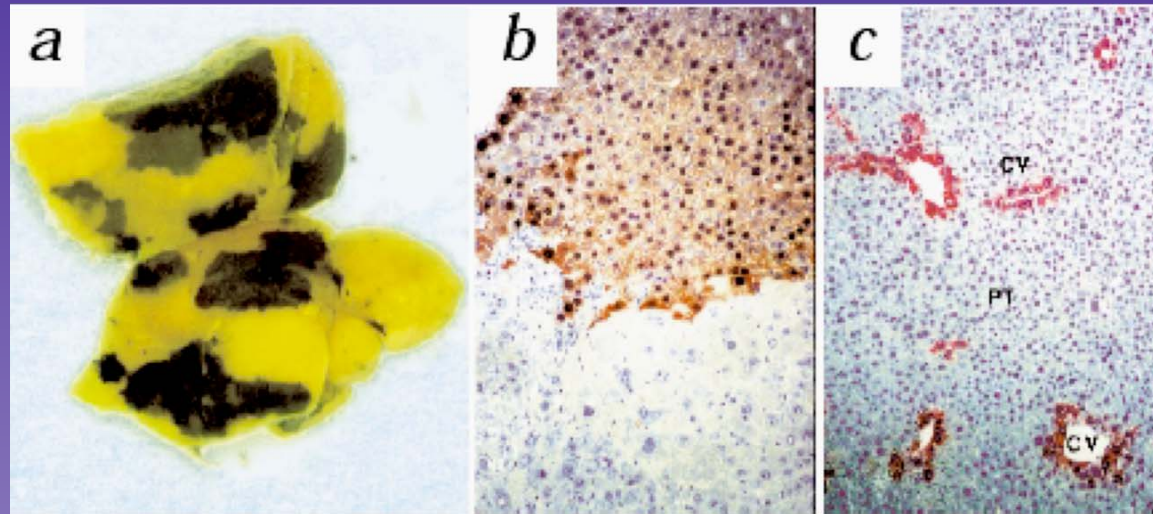
Reasons for limited success with BMT

1. The *mdx* phenotype is less severe than DMD
2. Satellite cells are not impaired by lack of dystrophin
3. Connective tissue may represent a barrier for blood born progenitors
4. Local microcirculation is reduced in dystrophic muscle
5. Vessel associated/circulating progenitors may have evolved for perinatal growth more than tissue repair

In certain cases things seem to work

Purified hematopoietic stem cells can differentiate into hepatocytes *in vivo*

Lagasse et al. Nature Medicine 6, 1129, 2000



Purified hematopoietic stem cells from Rosa 26 mice, form new hepatic lobules (blue) when injected into the portal vein of a FAH^{-/-} mouse that lacks a liver enzyme and undergoes massive liver necrosis when deprived of a replacement metabolite. In this case, **donor cells experience an immediate selective advantage over resident cells.**

Although stem cells appear able to differentiate in many different tissues, they are (not yet ?) efficacious in pre-clinical models for many genetic and acquired diseases.

Why ?

1. Stem cells must be in sufficient number within the tissue of origin (or they must be expandable in vitro).
2. Stem cells must be delivered efficaciously to the target tissue and must survive in it.
3. Stem cells must present a selective advantage over resident stem cells (when these are present).
4. Stem cells must differentiate in high percentage and functionally integrate within the target tissue.

Another example: stem cell appear to improve cardiac function after an infarct of the myocardium, but the mechanism is unclear.

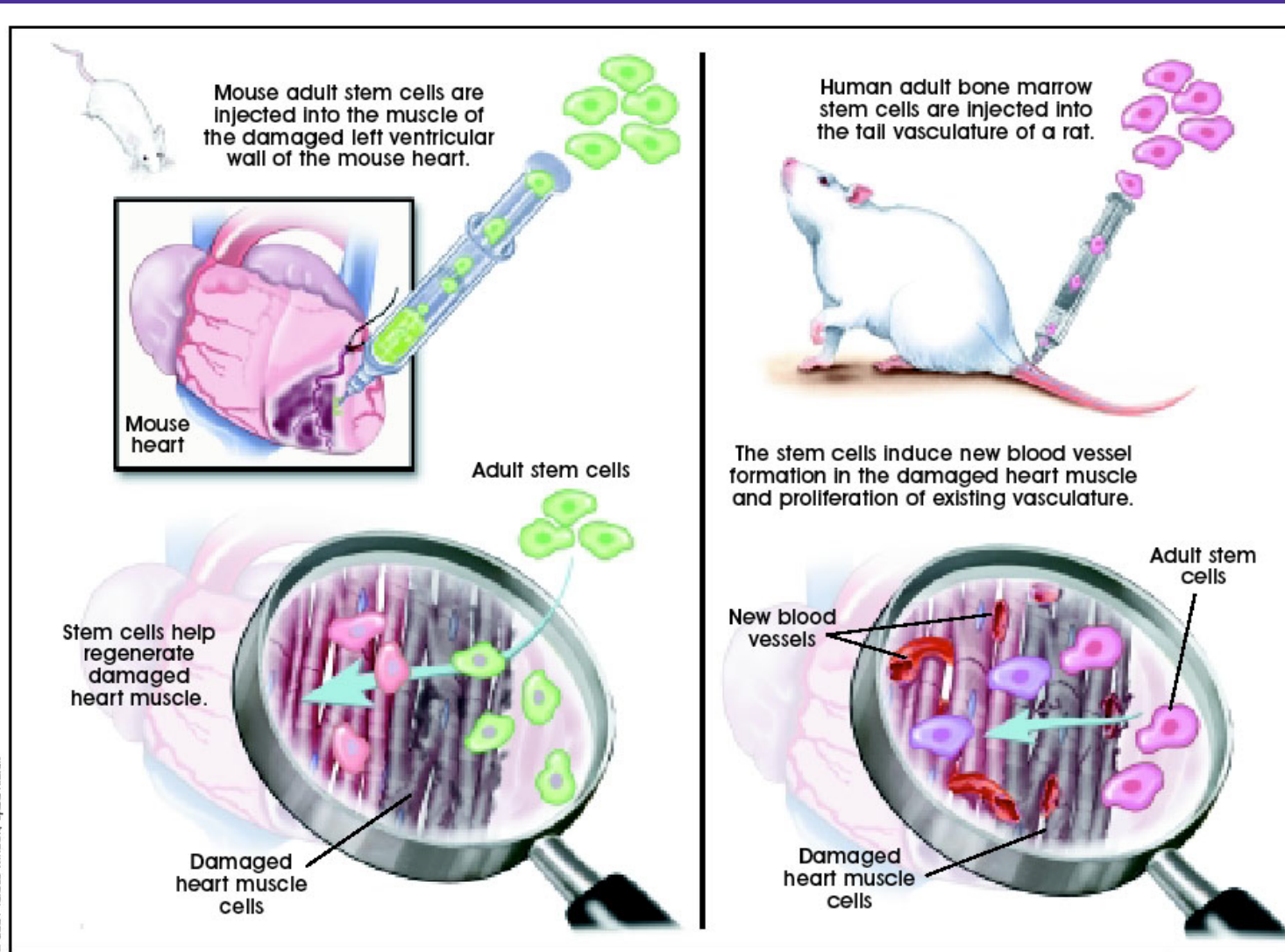


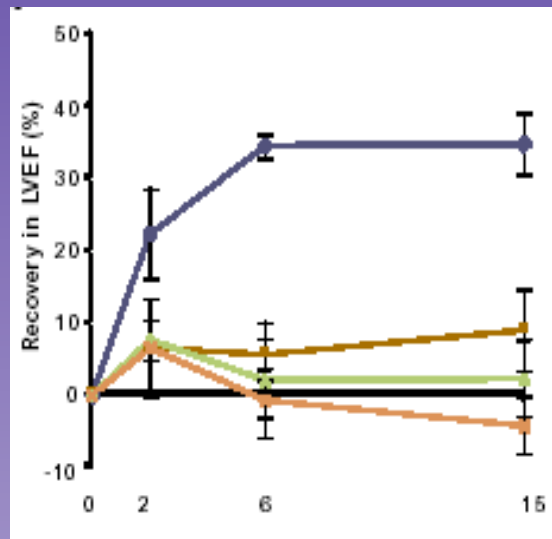
Figure 9.2. Heart Muscle Repair with Adult Stem Cells.

In uno studio del 2001, l'iniezione di cellule umane del midollo nel miocardio ischemico induce neovascolarizzazione, riduce la morte dei miocardiociti e migliora la funzione cardiaca

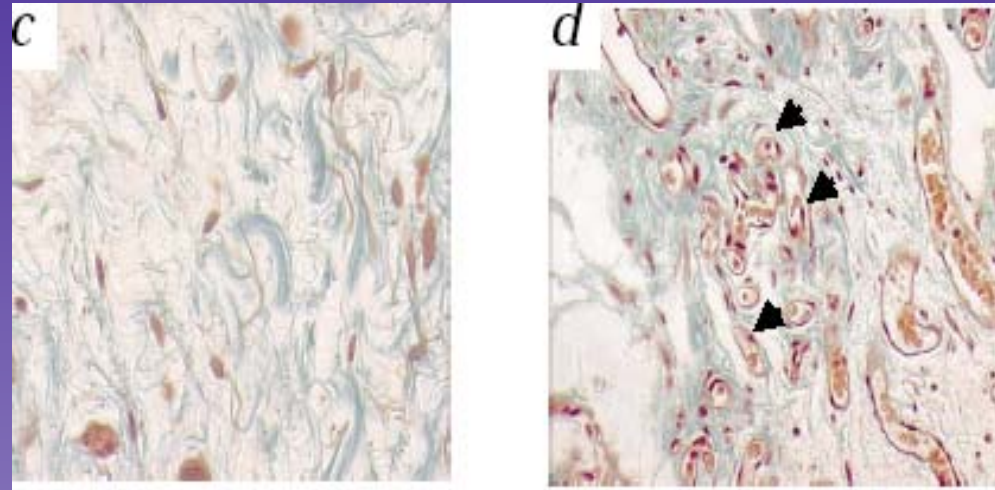
(Kocher et al. Nature Medicine 7, 430, 2001)

Aumentata vascolarizzazione

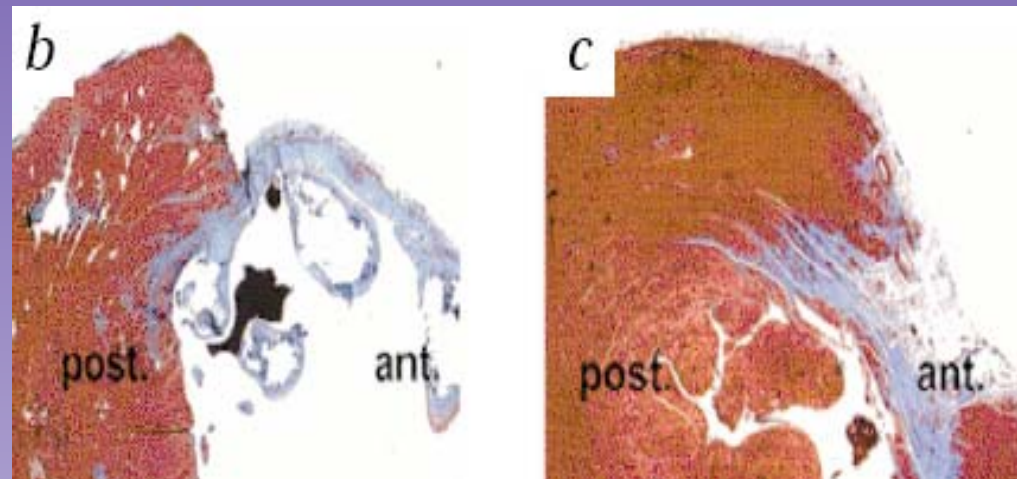
CD34+ umane furono iniettate nella regione perinfartuale del ventricolo sinistro



Recupero funzionale



Ridotta cicatrizzazione



Conclusioni:

1. Questo decennio ha modificato il nostro modo di pensare le cellule e i tessuti dei nostri organi.
2. Oggi possiamo riparare o ricostruire alcuni organi, domani forse molti ma per alcuni il percorso sarà lungo e difficile.
3. Questa ricerca ha un costo economico ma anche morale: molte companies sono pronte a investire per malattie comuni quali infarto o Alzheimer. Chi pagherà per la ricerca e le costose cure sperimentali di migliaia di malati colpevoli solo di essere stati colpiti da una malattia rara ?
4. Saprà il sistema sanitario nazionale confrontarsi con questa nuova situazione ?