



Christian
Doppler
Laboratory

for
Cardiac and Thoracic
Diagnosis & Regeneration



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Paracrine Mechanisms in Adult Stem Cell Signaling and Therapy

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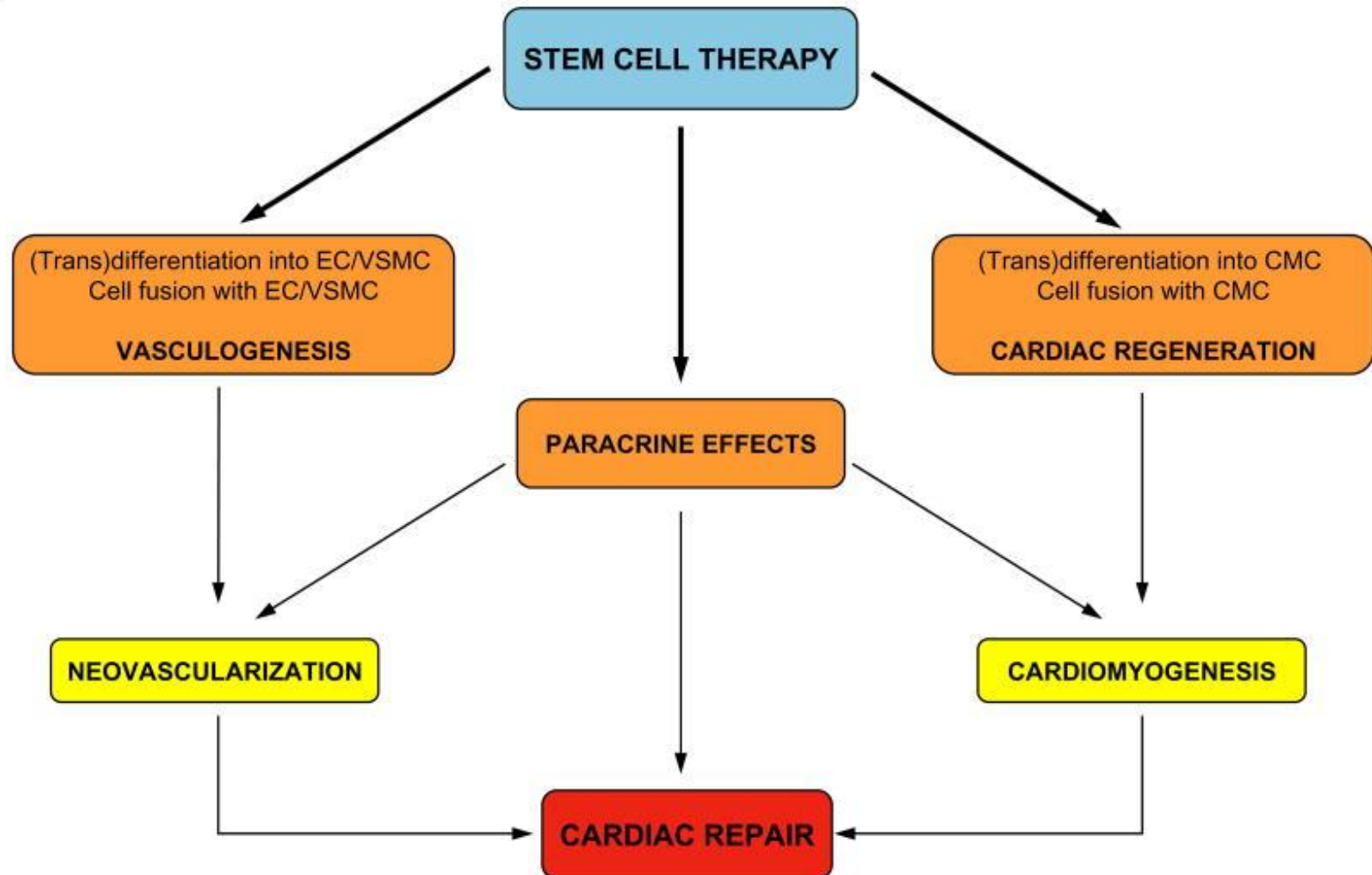
Introduction(1)

- After AMI all of the cardiac tissue served by the infarction related artery undergoes necrosis or apoptosis
- The endogenous regenerative capacity of the heart is not able to replenish a significant loss of tissue such as after AMI¹
- Therapeutic myocardial regeneration might be achieved by using adult stem cells (ASC)²

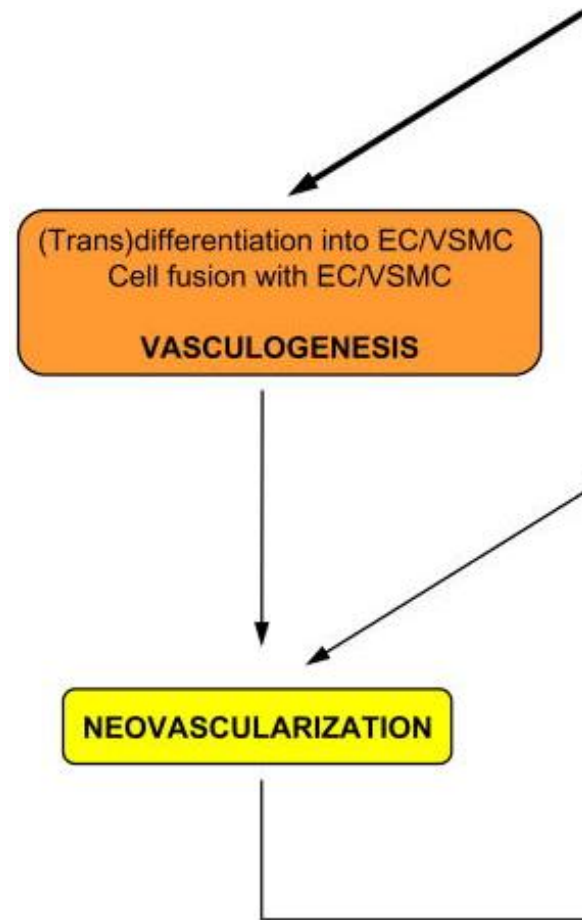
¹ Beltrami et al, *N Engl J Med* 2001;344:1750-1757

² Beltrami et al, *Cell* 2003;114:763-776

Stem Cell Therapy



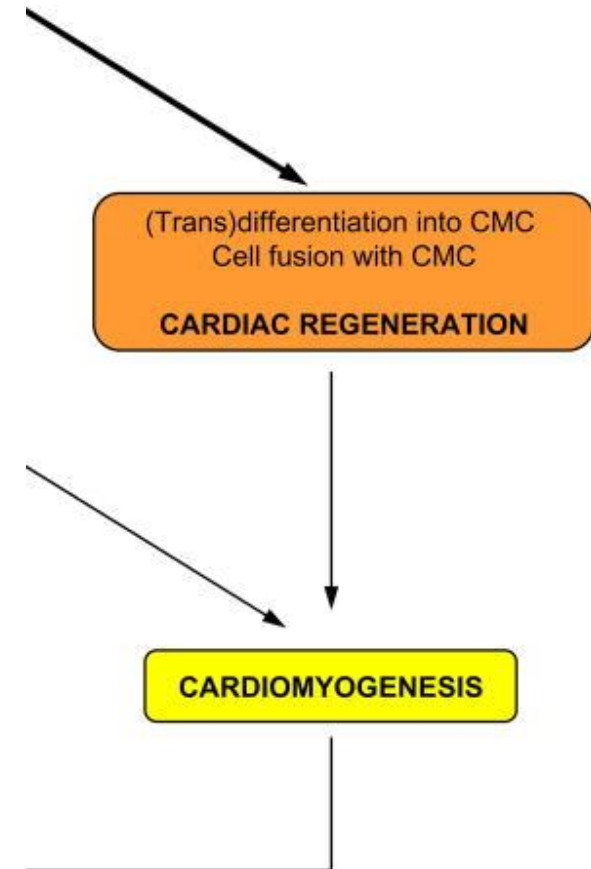
Stem Cell Therapy



Cardiac stem cells (CSC) – when injected into infarcted murine hearts – are able to differentiate into endothelial cells (EC) and vascular smooth muscle cells (VSMC)

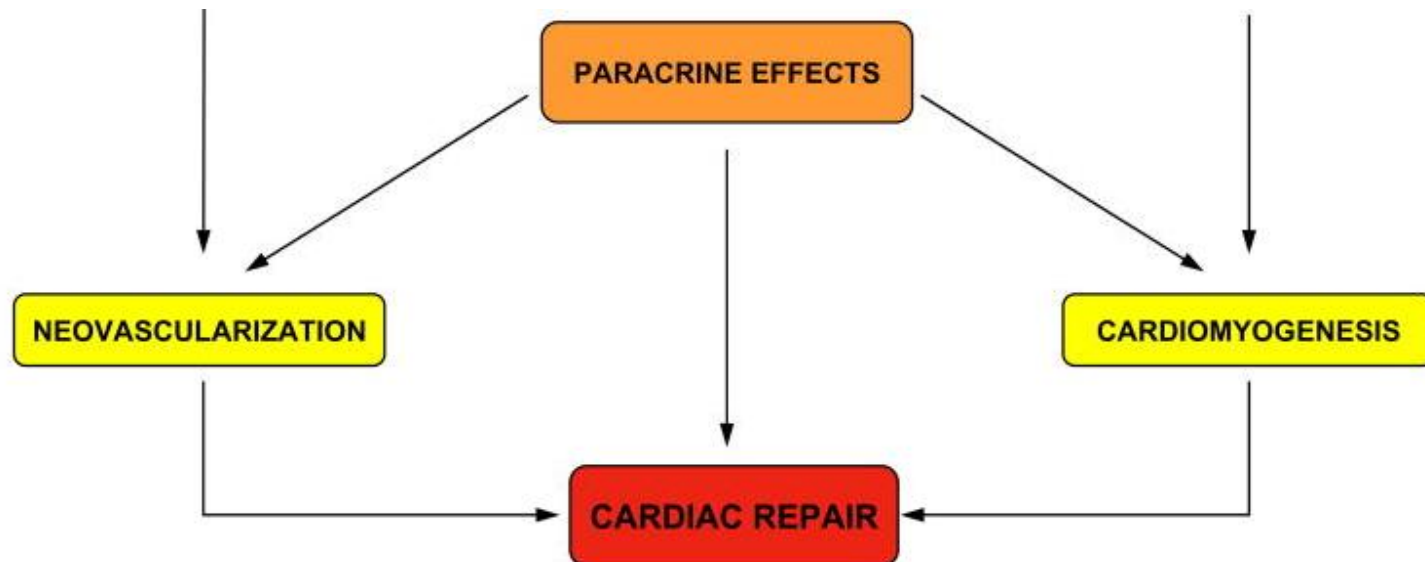
Stem Cell Therapy

Bone marrow derived stem cells injected into mouse hearts after AMI were able to engraft, transdifferentiate into cardiac cells and regenerate 60% of the infarcted area with newly formed cardiomyocytes

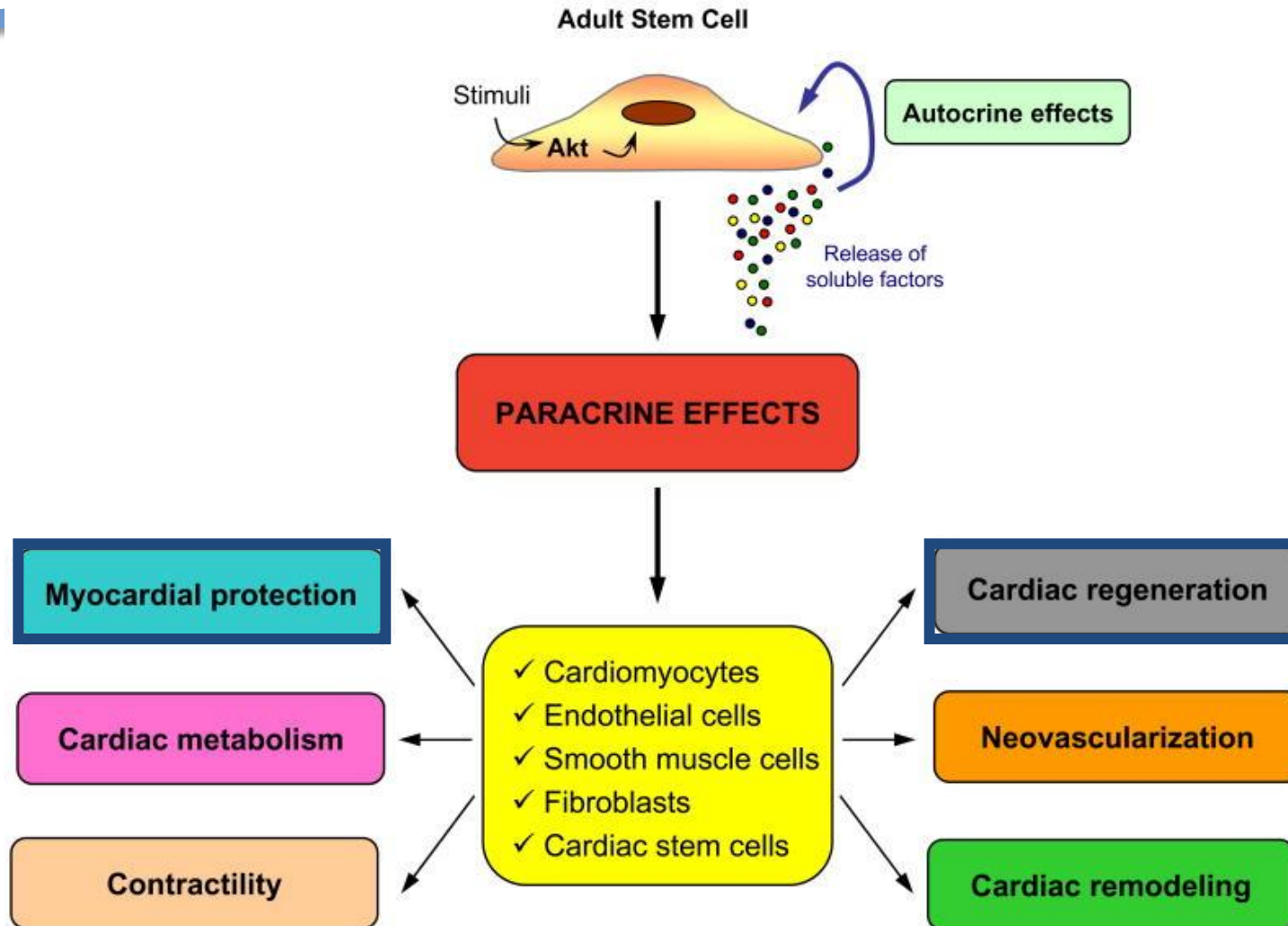


Stem Cell Therapy

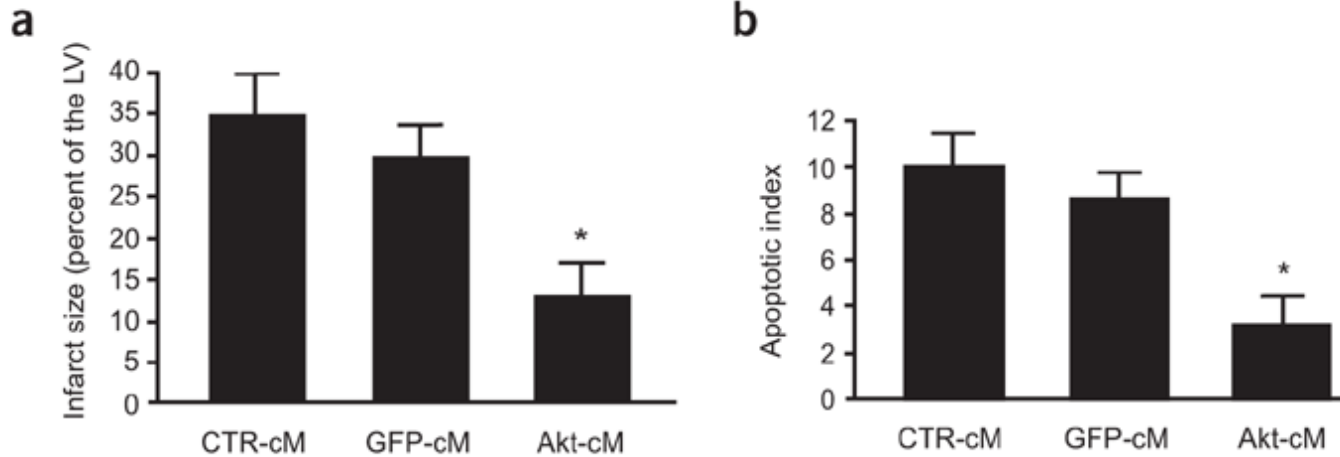
- It has been shown that the number of newly generated cardiomyocytes is too low to explain significant functional improvement¹
- The functional benefits might be related to secretion of soluble factors, acting in a paracrine fashion¹



Paracrine Effects



Myocardial Protection



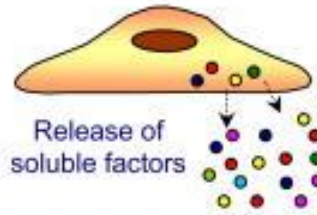
Myocardial Protection

Evaluation of some candidate genes encoding for molecules known to be released by MSC by **quantitative RT-PCR**

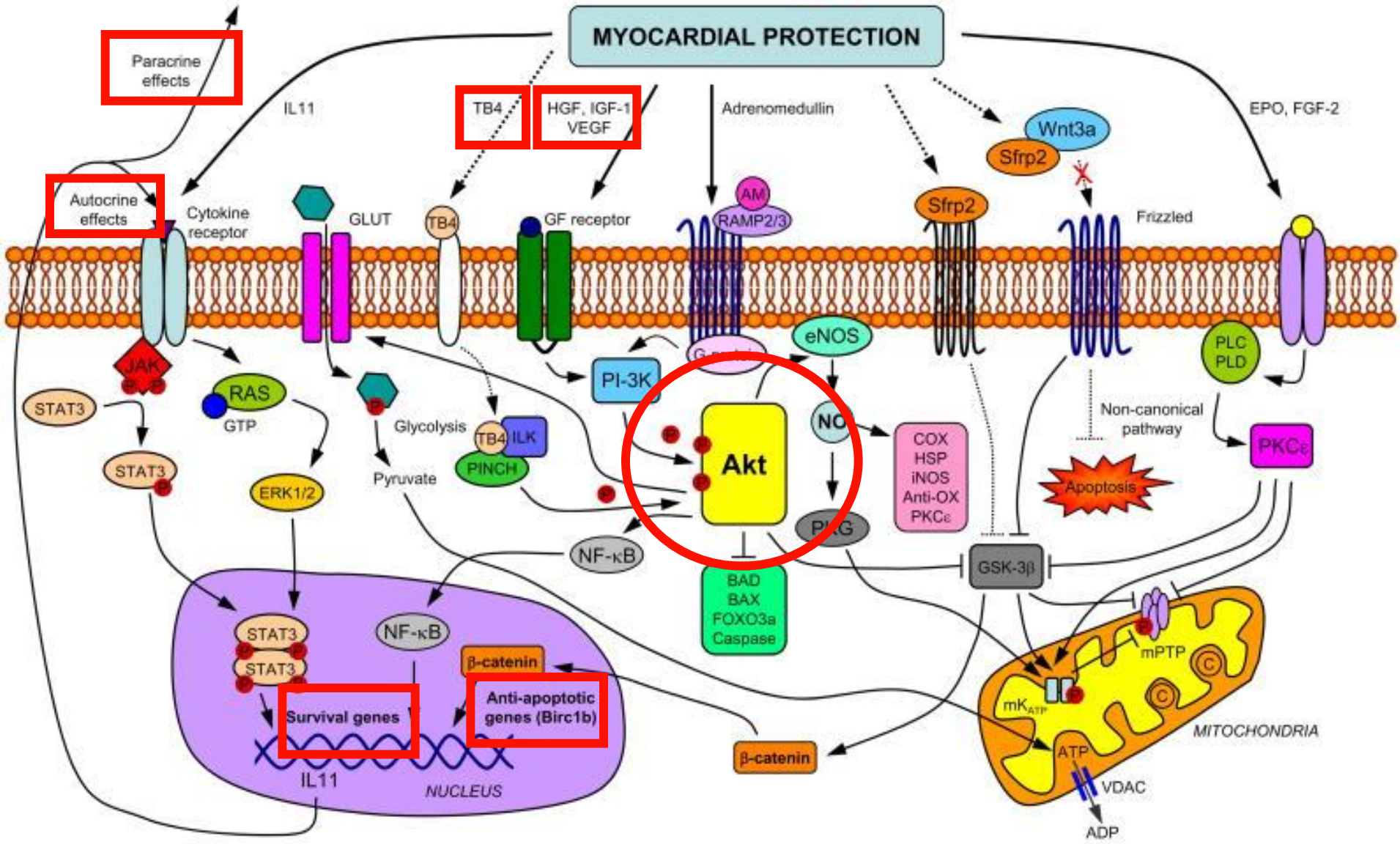


Significant upregulation of (in Akt-MSC):
VEGF, HGF, IGF-1, Thymosin beta-4

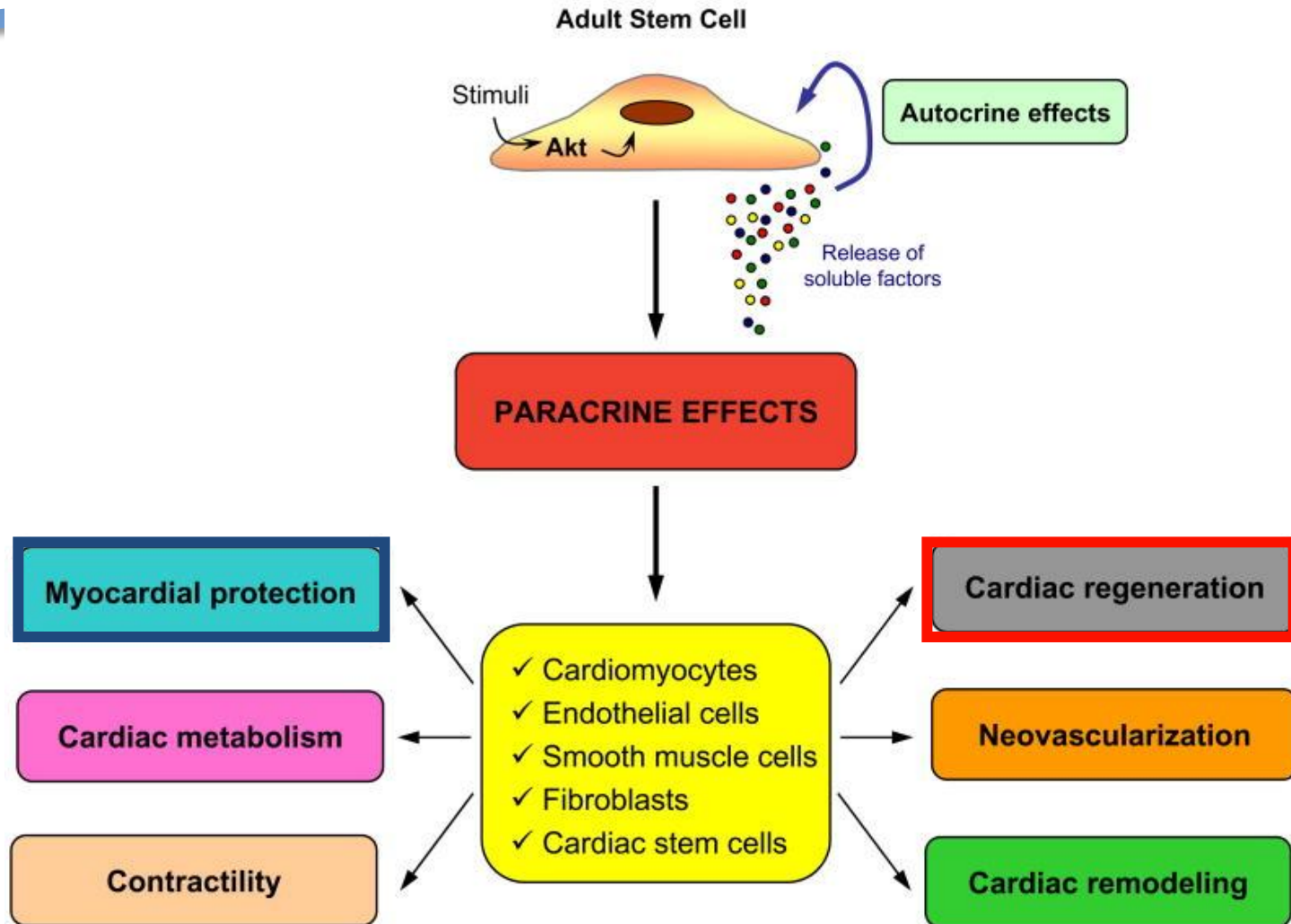
Adult Stem Cell



MYOCARDIAL PROTECTION



Paracrine Effects



Cardiac Regeneration

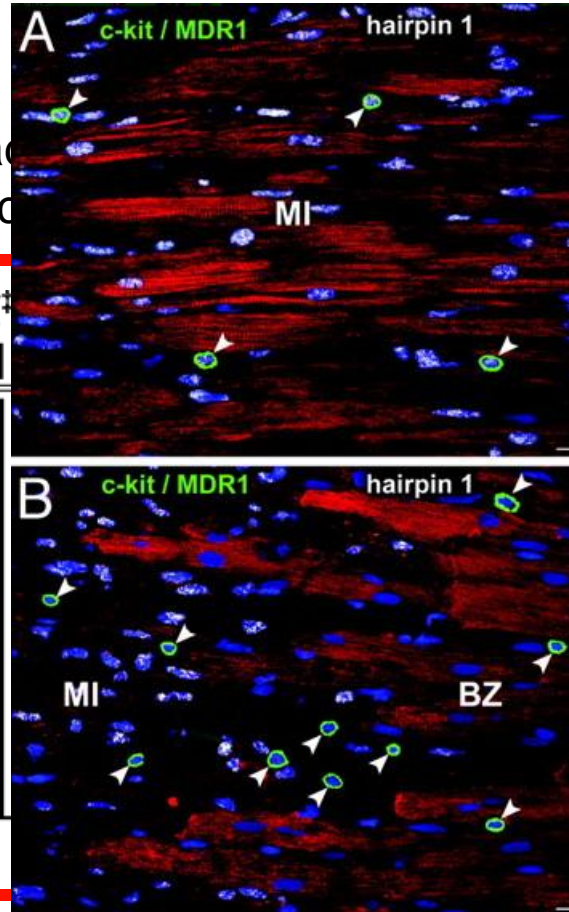
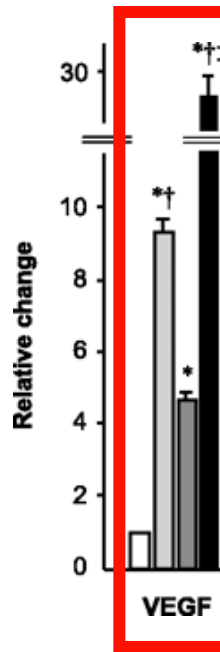
ASCs, when injected into the injured myocardium, are able to:

- Proliferate and transdifferentiate into cardiomyocytes¹
- Fuse with native cardiomyocytes and regenerate the lost myocardium¹
- Activate resident cardiac stem cells and stimulate cardiomyocytic replication via **paracrine action**

Cardiac Regeneration

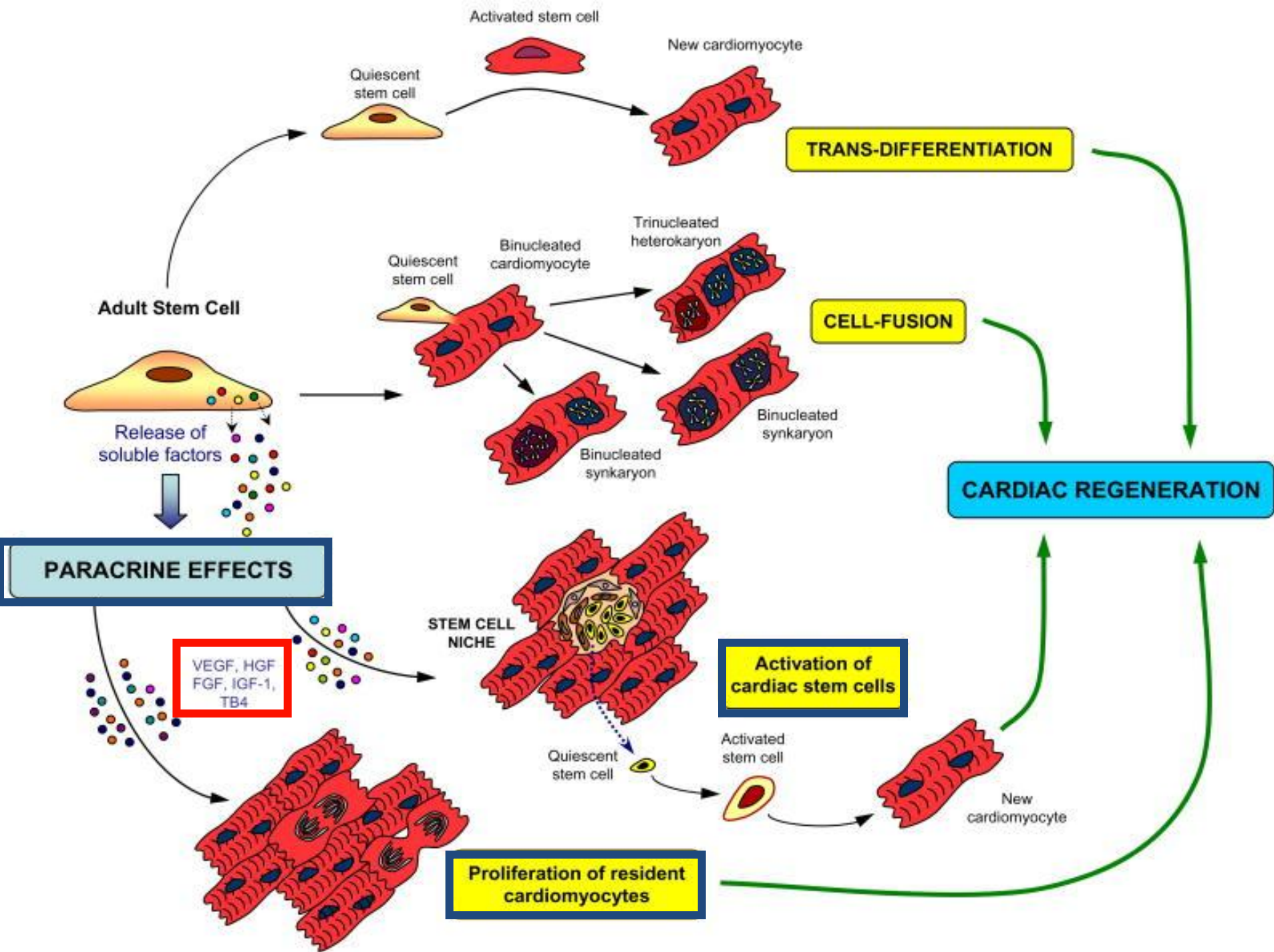
Intramyocardial and border zone induction of VEGF and IGF-1

and IGF-1 at the infarct border zone induce proliferation and differentiation¹



¹ Linke et al, Proc Natl Acad Sci U S A. 2005;102:8966–8971

² Gnechchi et al, FASEB J. 2006;20:661– 669.



Conclusion

- Transplantation of stem cells for their paracrine effects still represents a reasonable strategy – multiple factors might be functioning together
- If specific paracrine cell-derived factors will be identified protein based therapy might be more easily translated into clinical benefits than cell based therapy

Future in Stem Cell Therapy for the Heart

- Choice of cell type to administer: the cardiomyogenic potentiality of each ASC is not explored yet
- Extensive loss of the cells once transplanted in combination with the extreme rareness of specific stem cell populations
- Idea of improving cell survival by overexpressing protective genes: e.g. combination of genetic modification and preconditioning with different cytokines
- Cell administration immediately after infarction or after the inflammatory process has subsided?

Future in Stem Cell Therapy for the Heart

- Age of the patient and presence of disease status adversely influences characteristics of ASCs – using allogenic cells from young and healthy donors? Cell rejection? MSC display an immunoprivileged phenotype!¹
- Introduction of standard operating procedures and nomenclature among different laboratories will be mandatory to optimize our understanding of stem cell biology

Thank you for your attention!