Ankersmit Laboratory

for Diagnosis & Regeneration in Thoracic Diseases & Applied Immunology

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STEM CELLS FOR CARDIAC REGENERATION

REPLICABILITY OF SCIENTIFIC DATA

Lucian Beer *2016*

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OUTLINE

1. Stem cells for Cardiac regeneration (Orlic Paper)

2. Prof. Anversa´s group

3. Lessons to be learned

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Stem Cells for Cardiac Regeneration

"*Orlic paper*" published 2001 in *Nature*

- Showed that stem cells derived from bone marrow can transdifferentiate into cardiomyocytes and "*generate de nova myocardium*"
- (6032 citations on google scholar 05/2016)

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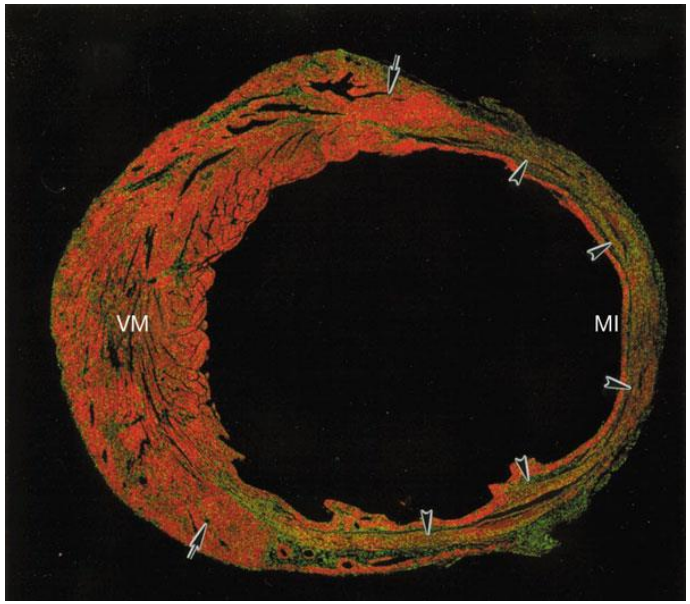
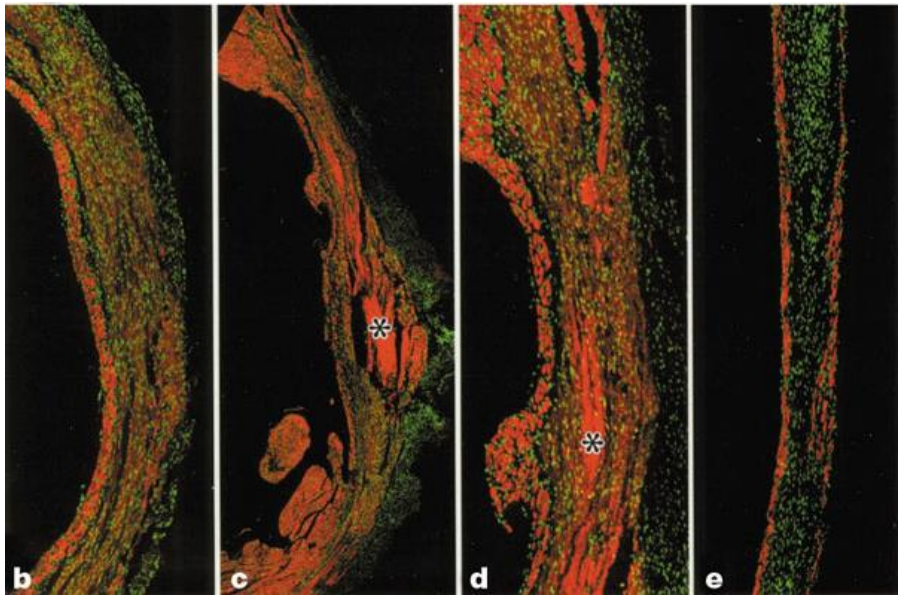
Stem Cells for Cardiac Regeneration





Myocardial infarct after injection on bone marrow derived stem cells. Arrowheads indicate regenerating myocardium; VM, viable myocardium.

red, cardiac myosin
green, propidium iodide labelling of nuclei

Orlic et al. *Nature* **410**, 701-705 (5 April 200

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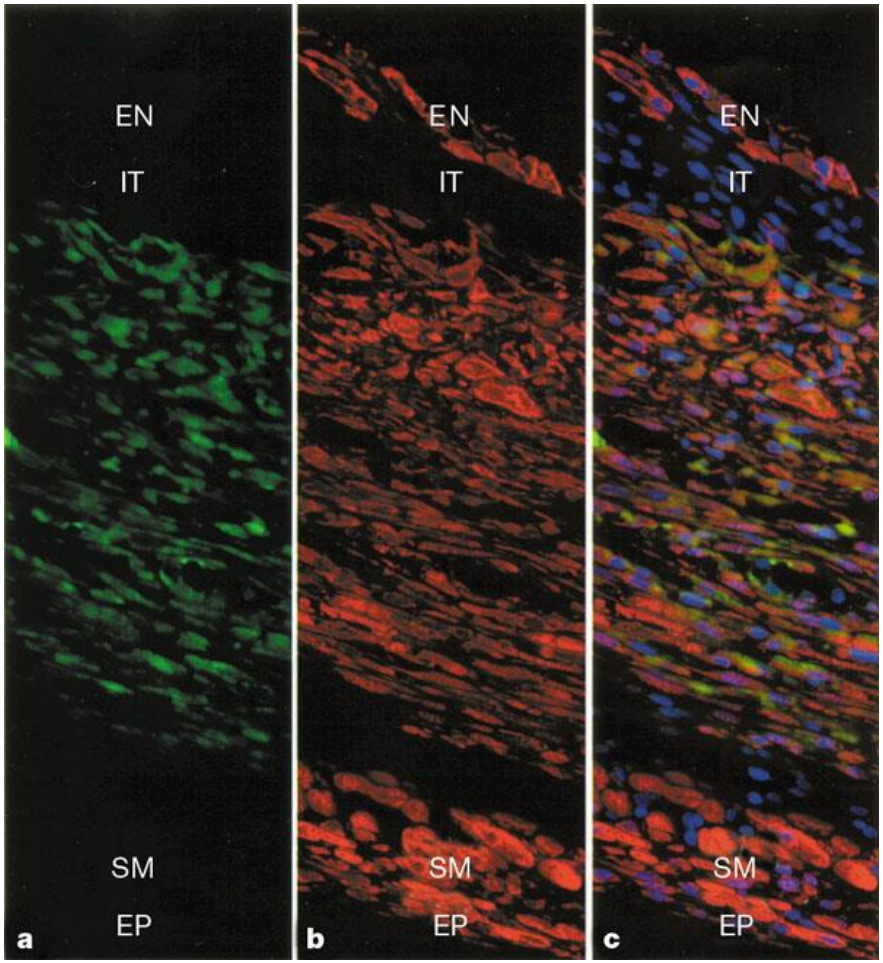
STEM CELLS

Stem cells regenerate the myocard from the endocardium (EN) to the epicardium (EP)



EGFP (green); **b**, cardiac myosin (red); **c**, combination of EGFP and myosin (red–green), and propidium-iodide-stained nuclei (blue).
Infarcted tissue (IT)
Subendocardial myocytes (SM)

Orlic et al. *Nature* **410**, 701-705 (5 April 200

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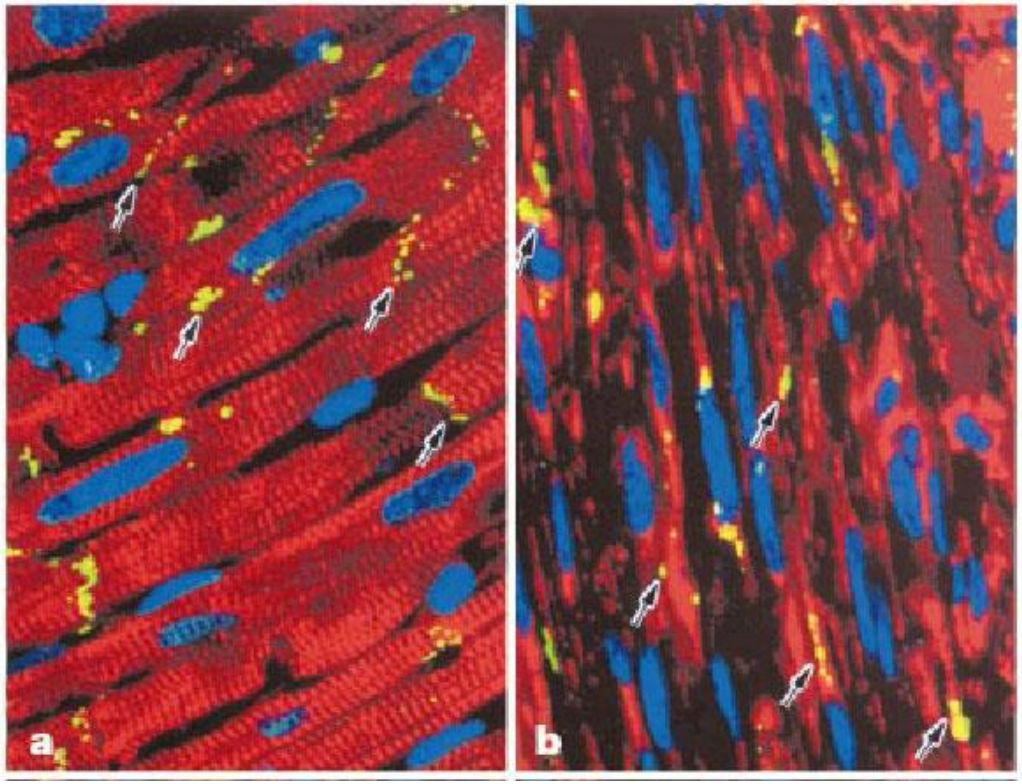
STEM CELLS

Newly built myocardium forms regular cell-cell contacts



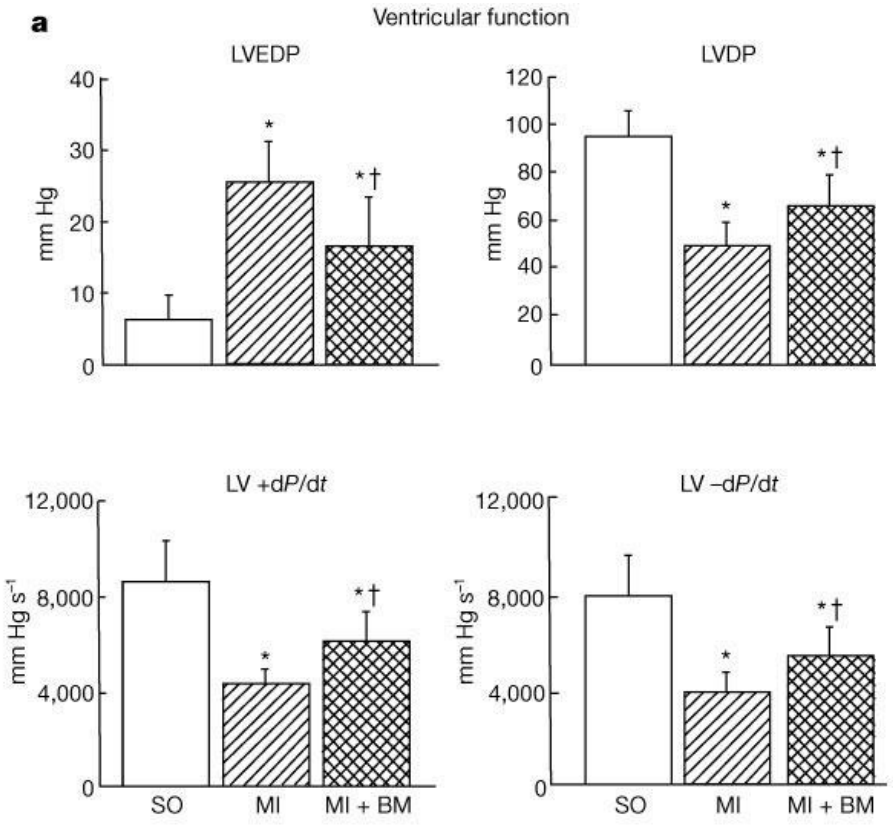
Border zone

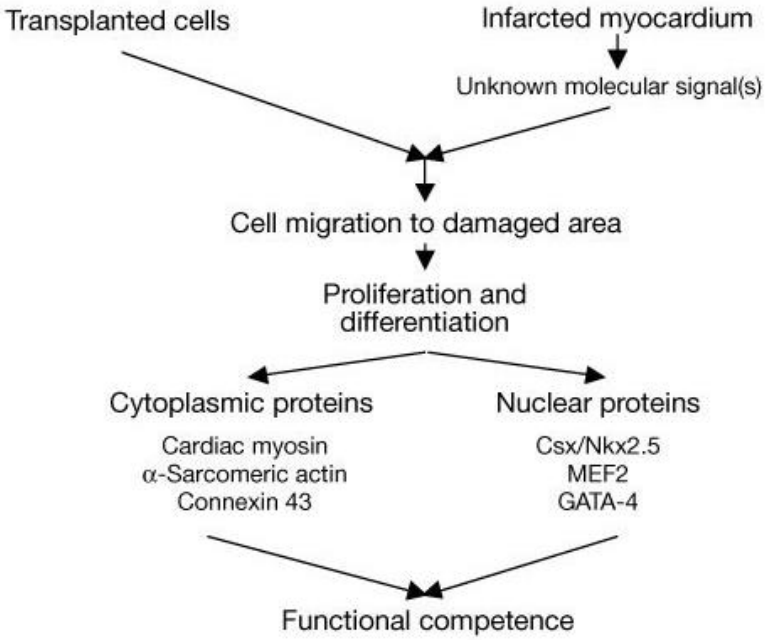
Area of regeneration

Orlic et al. *Nature* **410**, 701-705 (5 April 200

STEM CELLS

Stem cell improve cardic function





Proposed scheme

Orlic et al. *Nature* **410**, 701-705 (5 April 2001)

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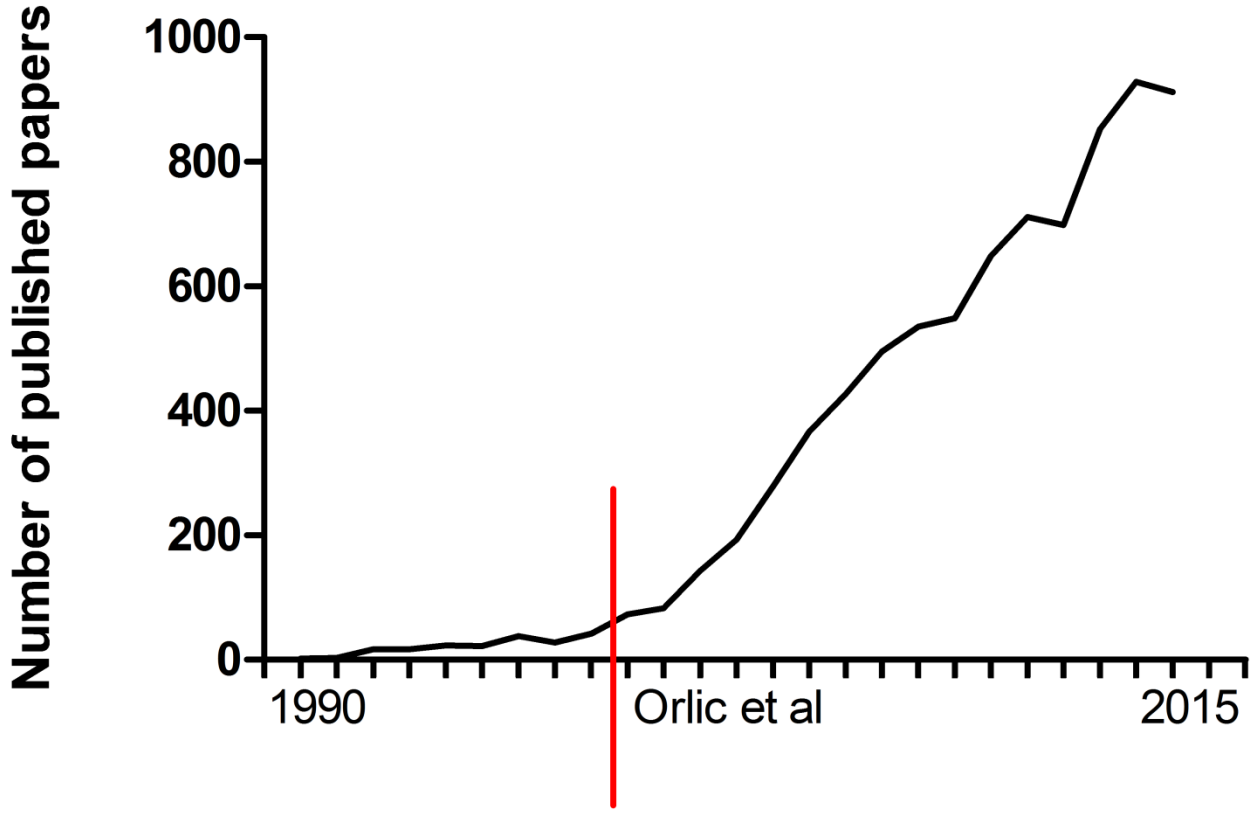
STEM CELLS



Pubmed search with tags: „stem cell“ AND heart

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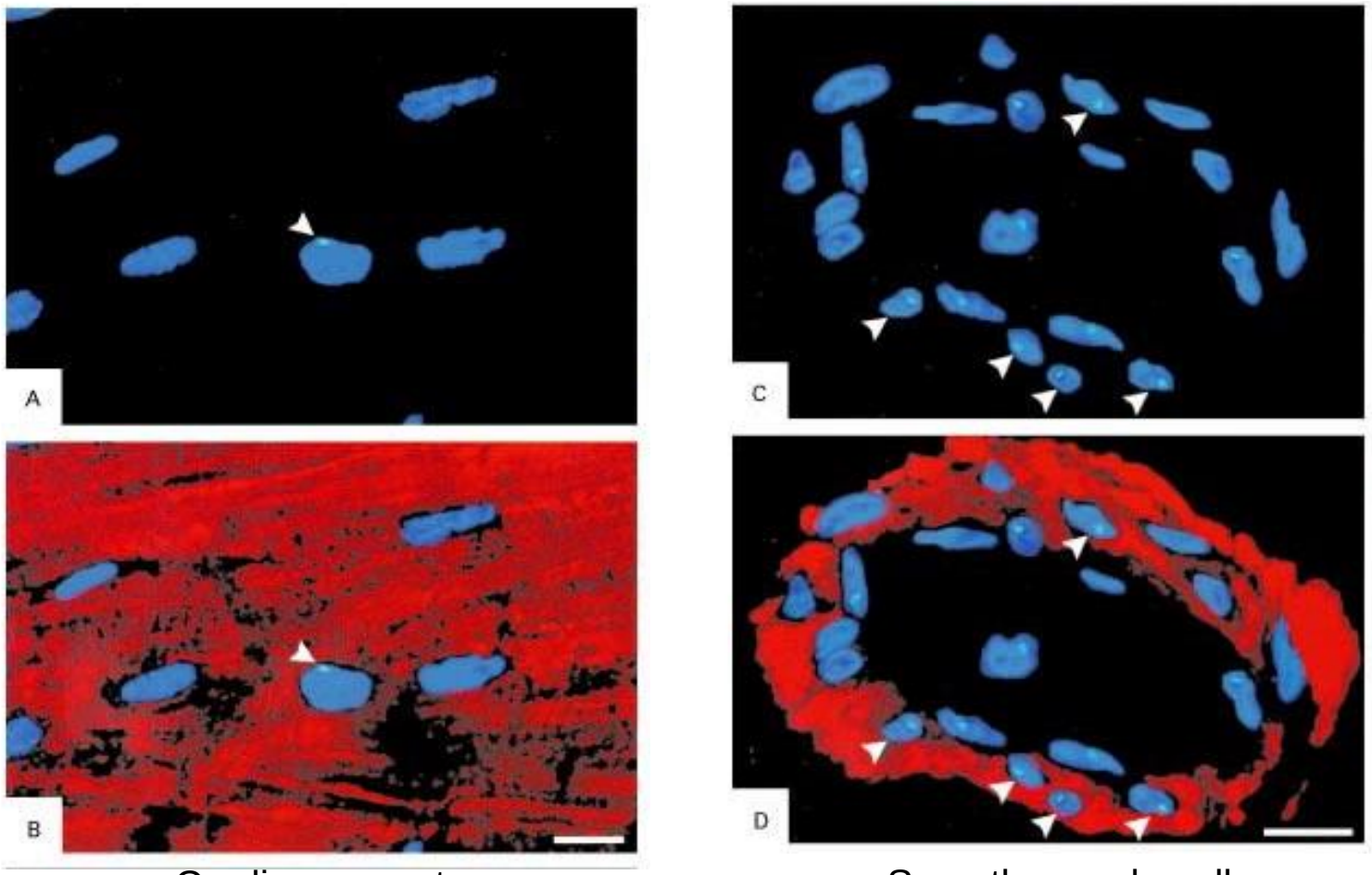
STEM CELLS HOME TO THE TRANSPLANTED HEART



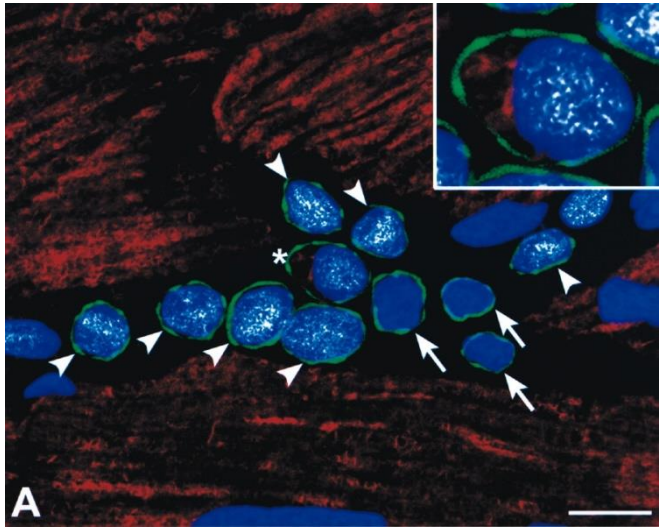
Cardiac myocytes

Smooth-muscle cells

Arrowhead = Y-chromosome in a female donor heart

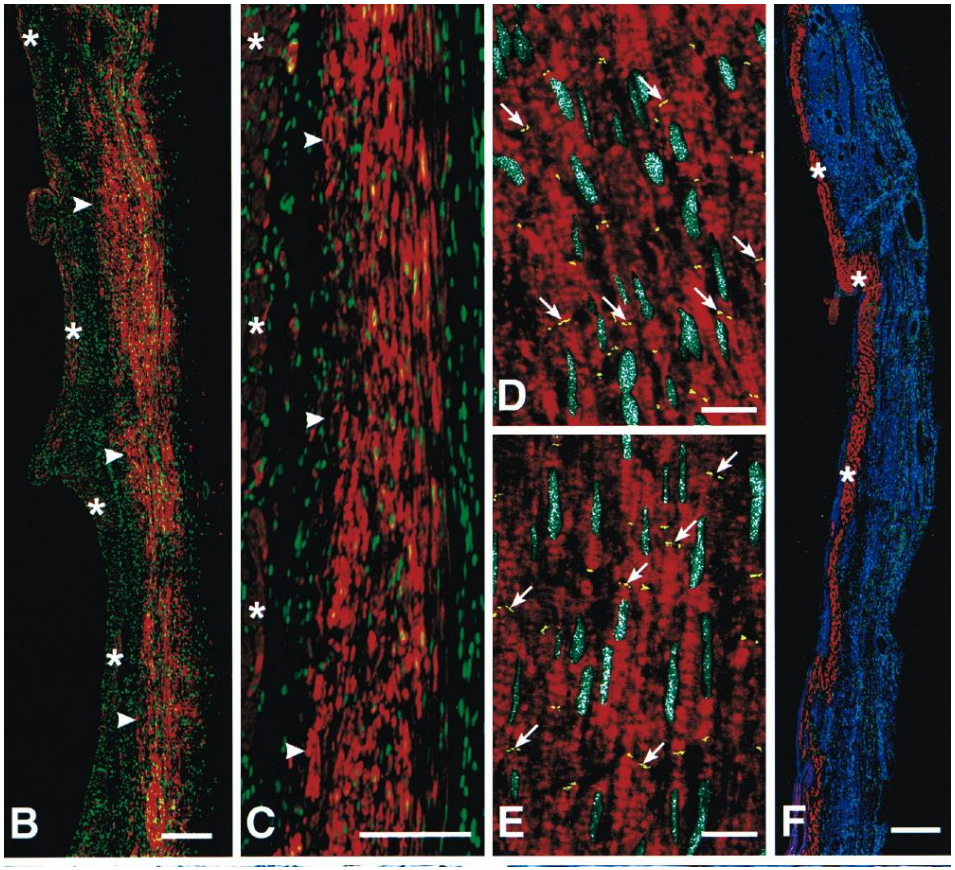
Quaini F et al. *N Engl J Med* 2002;**346**:5-15.

C-kit Cells are Cardiac Resident Cells



C-kit cells expressing the transcription factor Nkx2.5 (white dots)

In vivo data: 20 day after AMI;
Cardiac myosin, red; PI, green. (D) Connexin 43 (yellow; arrows). (E) N-cadherin (yellow; arrows). (D and E) BrdU-PI labeled nuclei, white-green



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

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CLINICAL IMPACT

Immediate tranlsation from basic science to clinical trials!

Study characteristics

Name of Study	Sample size (Cell therapy/ Controls)	Mean follow-up duration (month)	Cell type	Location of AMI	Time from AMI to cell delivery (days)	Imaging modality
CADUCEUS	17/8	12	Cardiosphere-derived cells	anterior (except 1)	62±11	MRI
BONAMI	52/49	3	BM-MNC	anterior	9±2	SPECT, RNV
Aalst Study	19/16	4	BM-MNC	multiple	12±1	LV Angiography
REPAIR-AMI	101/103	4	BM-MNC	multiple	4±1	LV Angiography
BOOST	30/30	6	BM-MNC	multiple	5±1	MRI
LATE-TIME	58/29	6	BM-MNC	multiple	17±5	MRI
ASTAMI	50/50	6	BM-MNC	anterior	6±1	SPECT, Echocard.
REGENT	160/40	6	BM-MNC, or selected CD34+CXCR	anterior	7±2	MRI
SWISS-AMI	133/67	4	BM-MNC	multiple	13±10	MRI
TIME	79/41	6	BM-MNC	multiple	5±2	MRI
SCAMI	29/13	12	BM-MNC	multiple	6±1	MRI
FINCELL	39/39	6	BM-MNC	multiple	3±1	Echocard.

SPECT: single photon emission computed tomography, RNV: radionuclide ventriculography; Echocard.: Echocardiography

Gyöngyösi et al. *Circ Res* 2015

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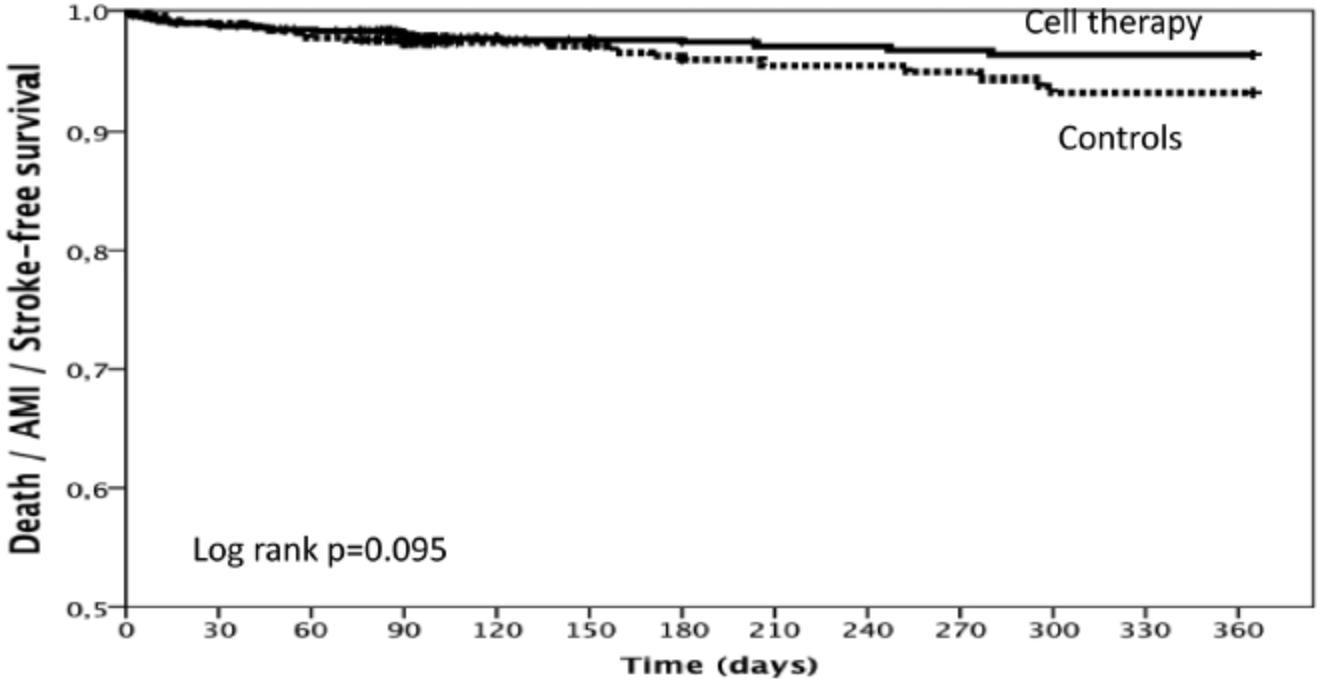
CLINICAL IMPACT



Cell-treated	767	754	746	701	567	473	272	270	270	269	268	268	267 Number left
	0	9	12	15	17	16	19	20	20	21	22	22	22 Number event
Controls	485	479	472	399	362	342	182	181	181	180	177	177	176 Number left
	0	5	11	13	13	14	18	19	19	20	23	23	23 Number event

Gyöngyösi et al. *Circ Res* 2015

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Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts

Charles E. Murry[1], Mark H. Soonpaa[2], Hans Reinecke[1], Hidehiro Nakajima[2], Hisako O. Nakajima[2], Michael Rubart[2], Kishore B. S. Pasumarthi[2*], Jitka Ismail Virag[1], Stephen H. Bartelmez[3], Veronica Poppa[1], Gillian Bradford[2], Joshua D. Dowell[2], David A. Williams[2*] & Loren J. Field[2]

NATURE | VOL 428 | 8 APRIL 2004 | www.nature.com/nature

several clinical trials[16,17]. Here, we used both cardiomyocyte-restricted and ubiquitously expressed reporter transgenes to track the fate of haematopoietic stem cells after 145 transplants into normal and injured adult mouse hearts. No transdifferentiation into cardiomyocytes was detectable when using these genetic techniques to follow cell fate, and stem-cell-engrafted hearts showed no overt increase in cardiomyocytes compared to sham-engrafted hearts. These results indicate that haematopoietic stem cells do not readily acquire a cardiac phenotype, and raise a cautionary note for clinical studies of infarct repair.

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OUTLINE

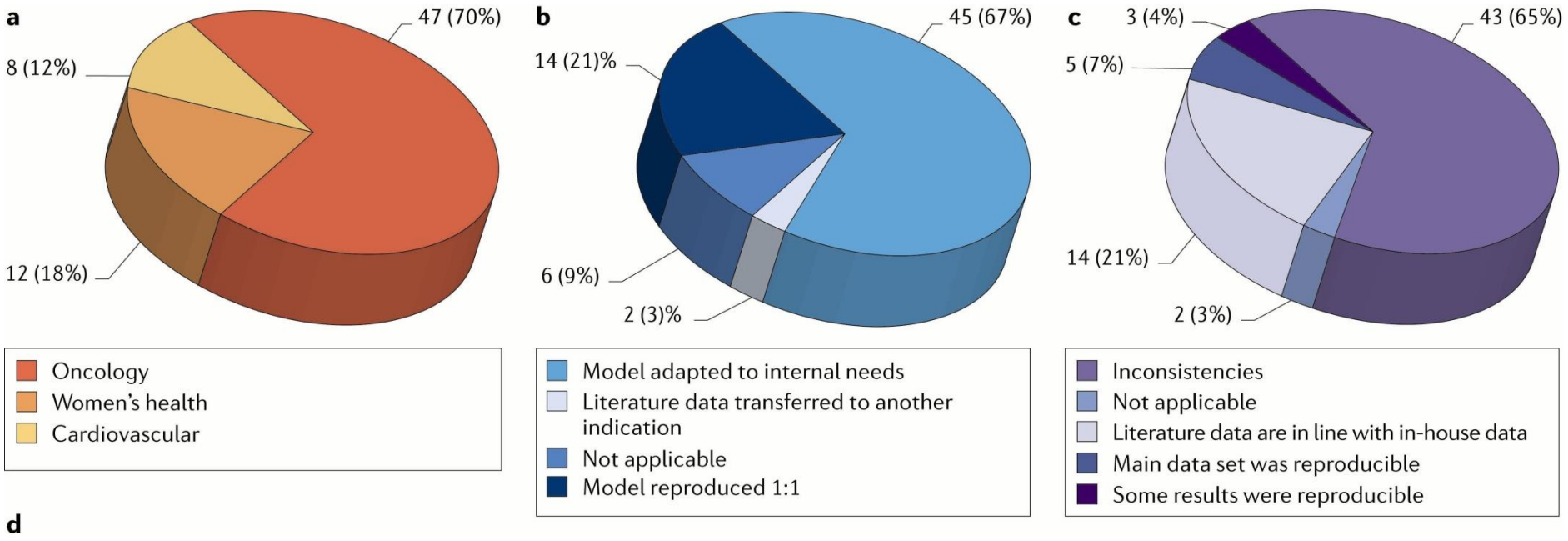
1. Stem cells for Cardiac regeneration (Orlic Paper)

2. Prof. Anversa´s group

3. Lessons to be learned

LESSONS TO BE LEARNED

1. Reproducibility of scientific data is <50%
   - No correlation between IF and reproducibility



Prinz et al. *Nature Reviews Drug Discovery*2011 ;**10**

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LESSONS TO BE LEARNED

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Table 1. Examples of Some Reported Reproducibility Concerns in Preclinical Studies

Author	Field	Reported Concerns
Ioannidis et al (2009)[22]	Microarray data	16/18 studies unable to be reproduced in principle from raw data
Baggerly et al (2009)[23]	Microarray data	Multiple; insufficient data/poor documentation
Sena et al (2010)[24]	Stroke animal studies	Overt publication bias: only 2% of the studies were negative
Prinz (2011)[1]	General biology	75% to 80% of 67 studies were not reproduced
Begley & Ellis (2012)[2]	Oncology	90% of 53 studies were not reproduced
Nekrutenko & Taylor(2012)[25]	NGS data access	26/50 no access to primary data sets/software
Perrin (2014)[26]	Mouse, in-vivo	0/100 reported treatments repeated positive in studies of ALS
Tsilidis et al (2013)[27]	Neurological studies	Too many significant results, overt selective reporting bias
Lazic & Essioux (2013)[28]	Mouse VPA model	Only 3/34 used correct experimental measure
Haibe-Kains et al (2013)[29]	Genomics/cell line analysis	Direct comparison of 15 drugs and 471 cell lines from 2 groups revealed little/no concordant data
Witwer (2013)[30]	Microarray data	93/127 articles were not MIAME compliant
Elliott et al (2006)[31]	Commercial antibodies	Commercial antibodies detect wrong antigens
Prassas et al (2013)[32]	Commercial ELISA	ELISA Kit identified wrong antigen
Stodden et al (2013)[33]	Journals	Computational biology: 105/170 journals noncompliant with National Academies recommendations
Baker et al (2014)[34]	Journals	Top tier fail to comply with agreed standards for animal studies
Vaux (2012)[35]	Journals	Failure to comply with their own statistical guidelines

ALS indicates amyotrophic lateral sclerosis; MIAME, minimum information about a microarray experiment; NGS, next generation sequencing; and VPA, valproic acid (model of autism).

Prinz et al. *Nature Reviews Drug Discovery*2011 ;**10**

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LESSONS TO BE LEARNED

1. Reproducibility of scientific data is <50%
   - No correlation between IF and reproducibility
2. Publishing policies (e.g.. Publication pressure, splitting of data analysis – PI does all final data analysis…)
3. Academic culture:
   - Journal clubs
   - Cooperation
   - Publishing of raw data….

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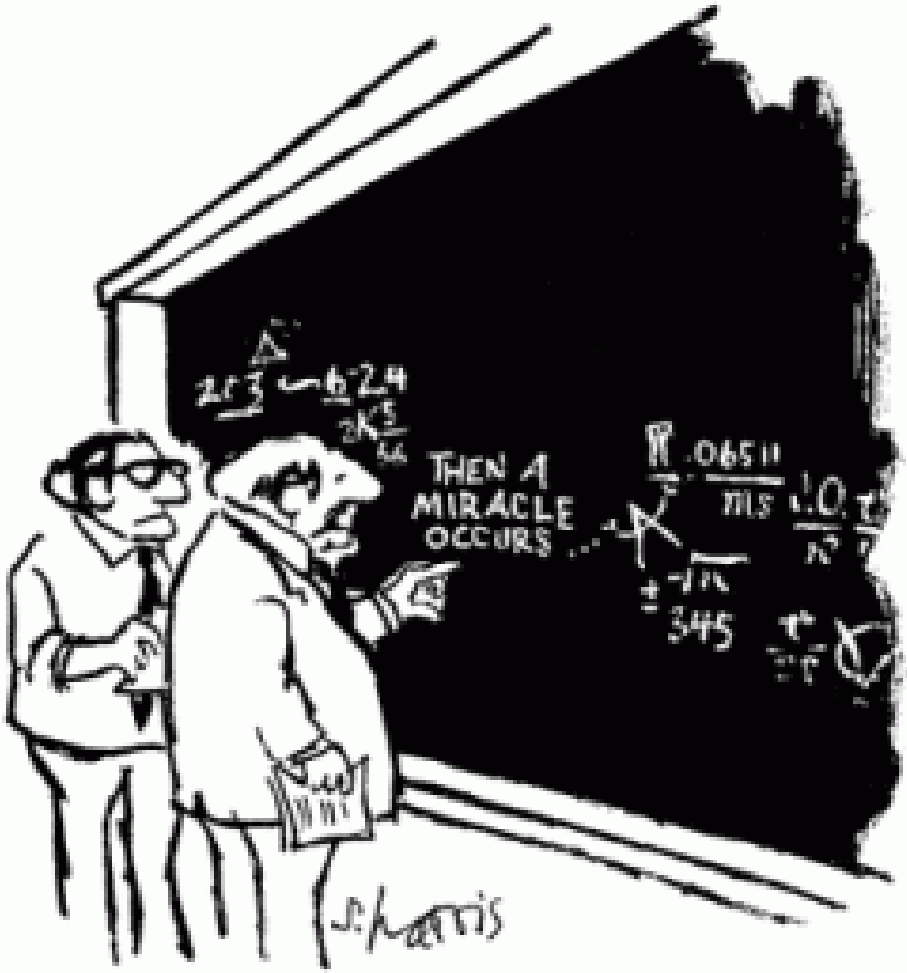
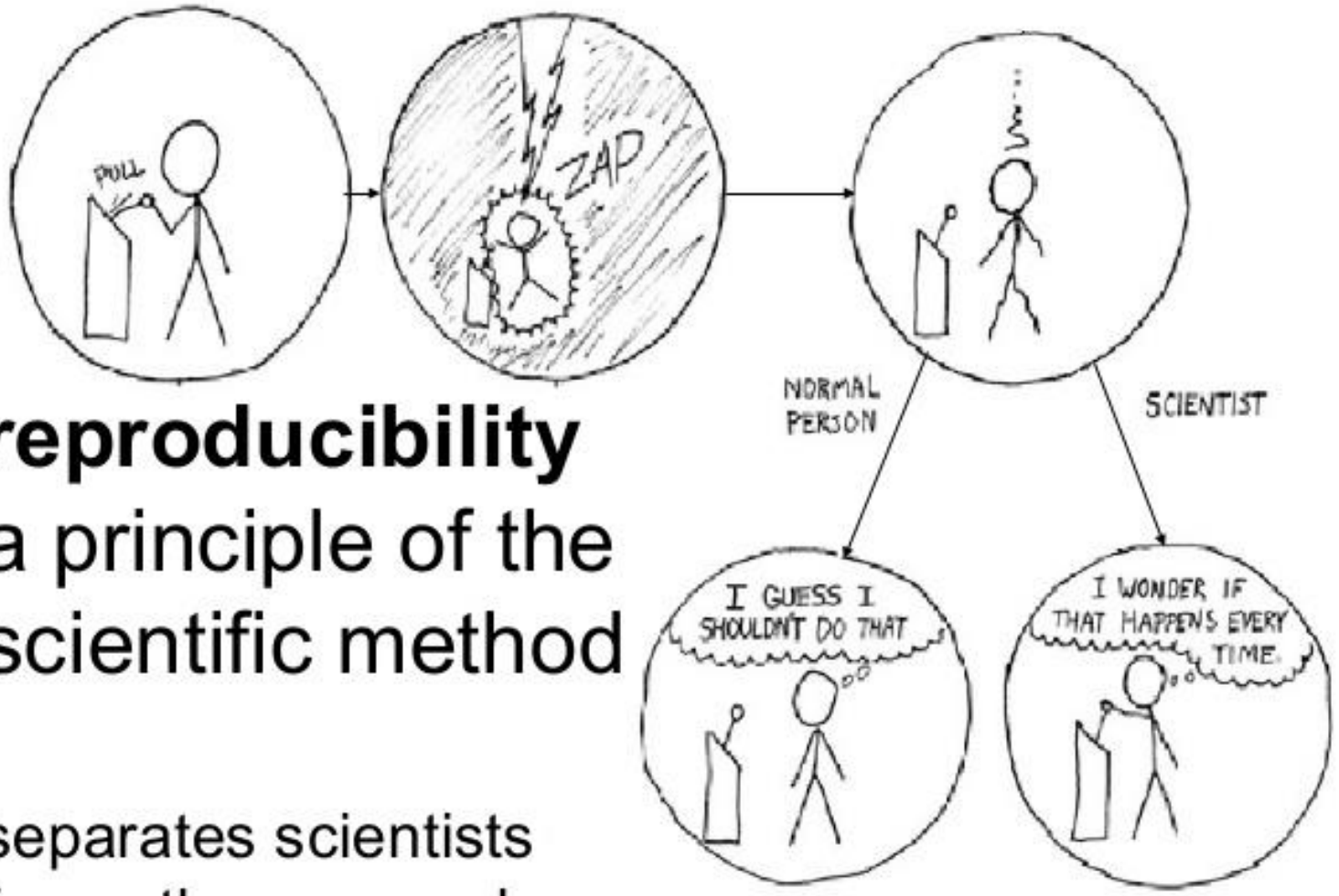
CONCLUSION



"I think you should be more explicit here in step two."

http://www.huffingtonpost.com/david-h-bailey/set-the-default-to-open-r_b_2635850.html



reproducibility
a principle of the scientific method

separates scientists from other researchers and normal people

http://xkcd.com/242/