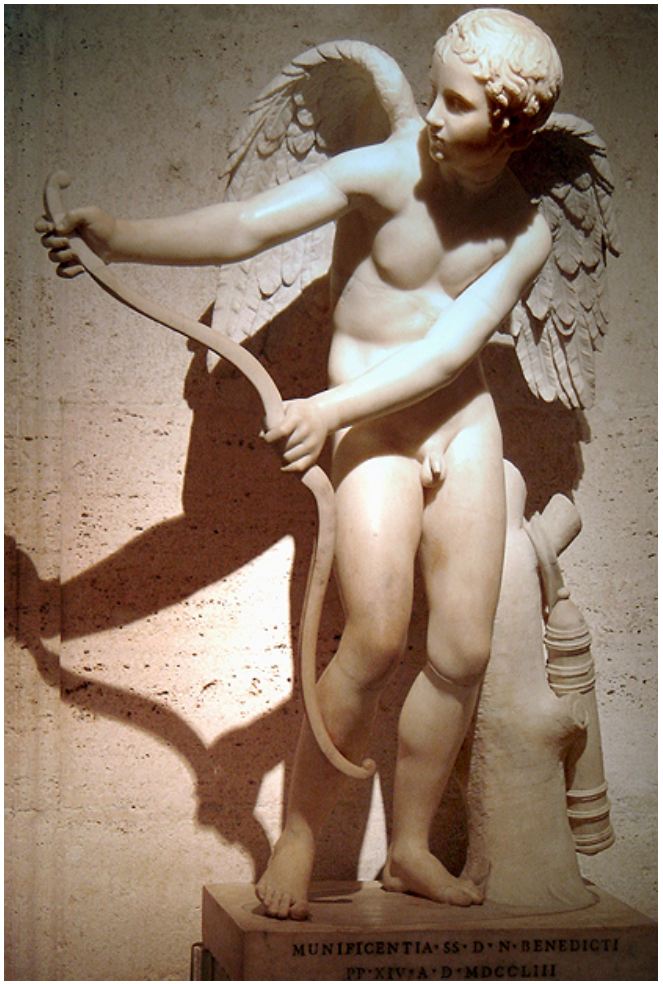
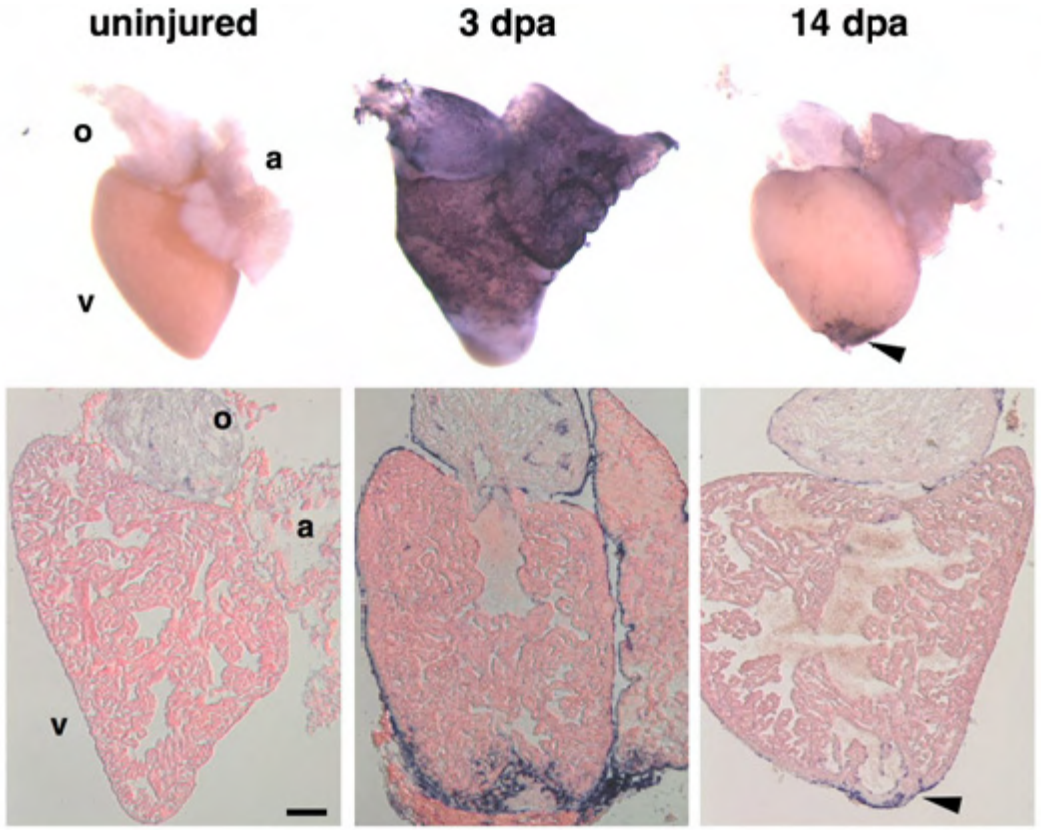
MiRNAs in CARDIAC REGENERATION

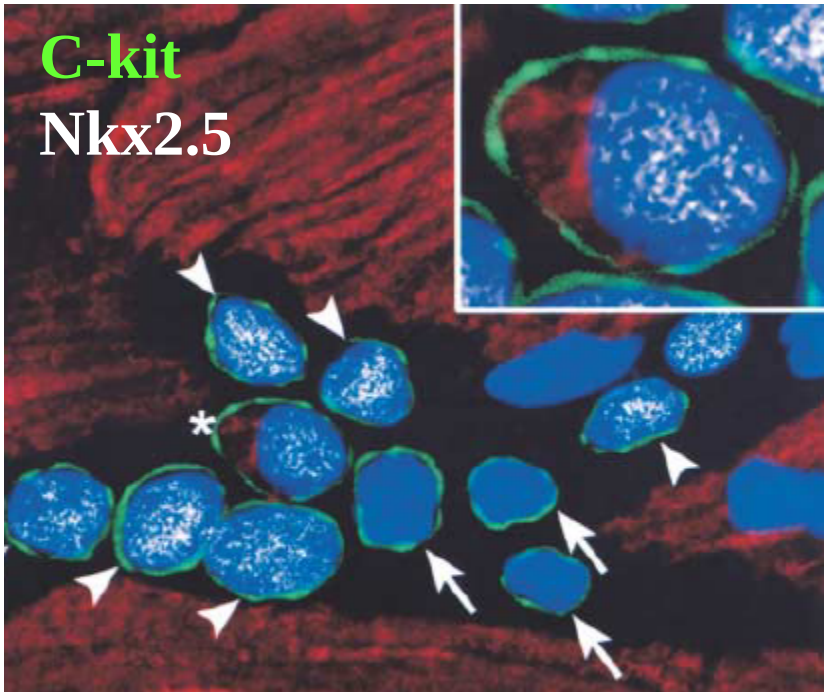
MiRNAs in CARDIAC REGENERATION

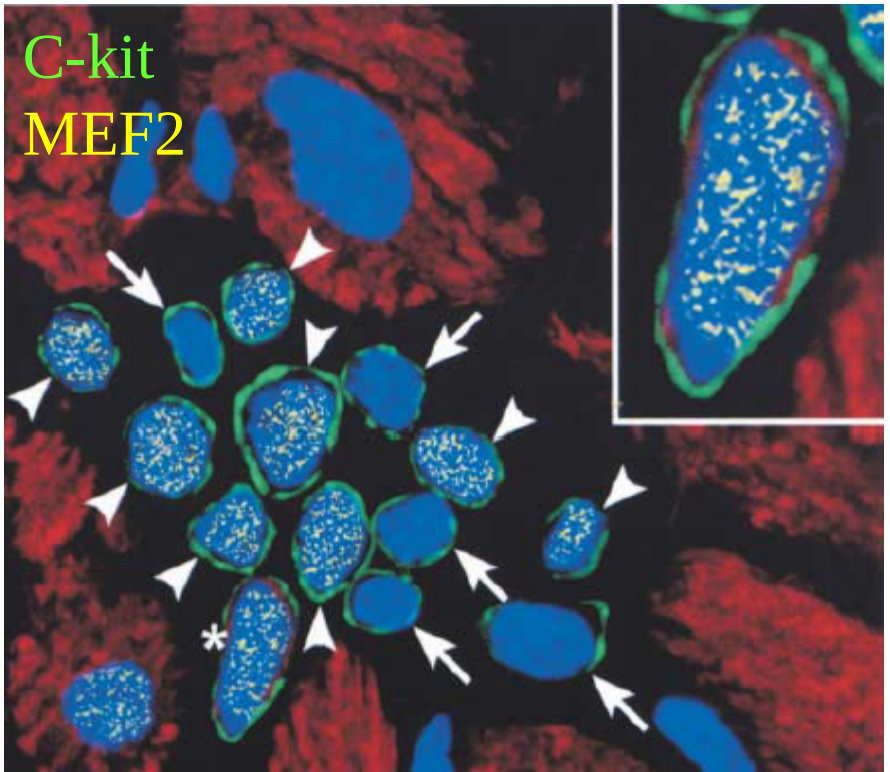




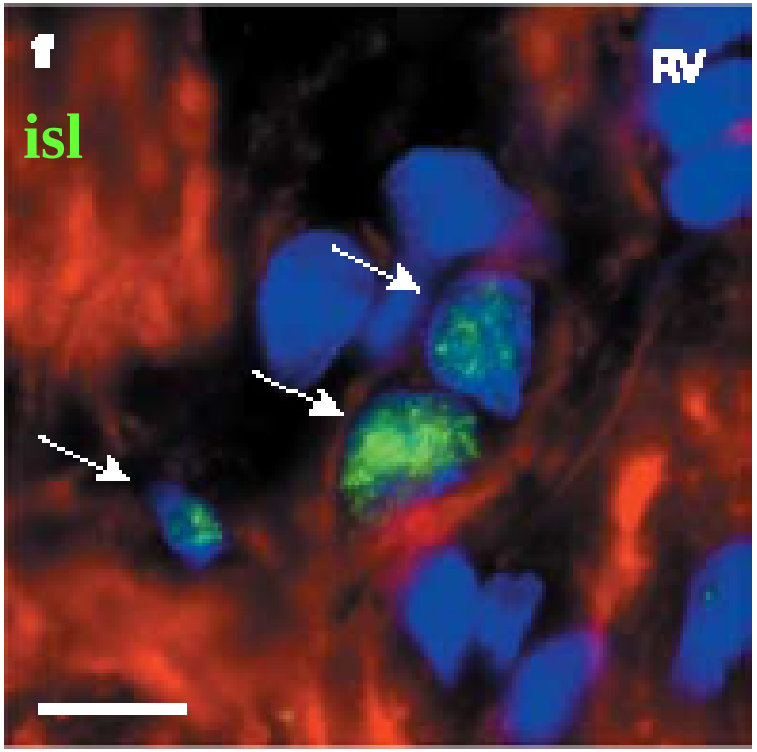
Lepilina et al Cell 2006; 127: 607

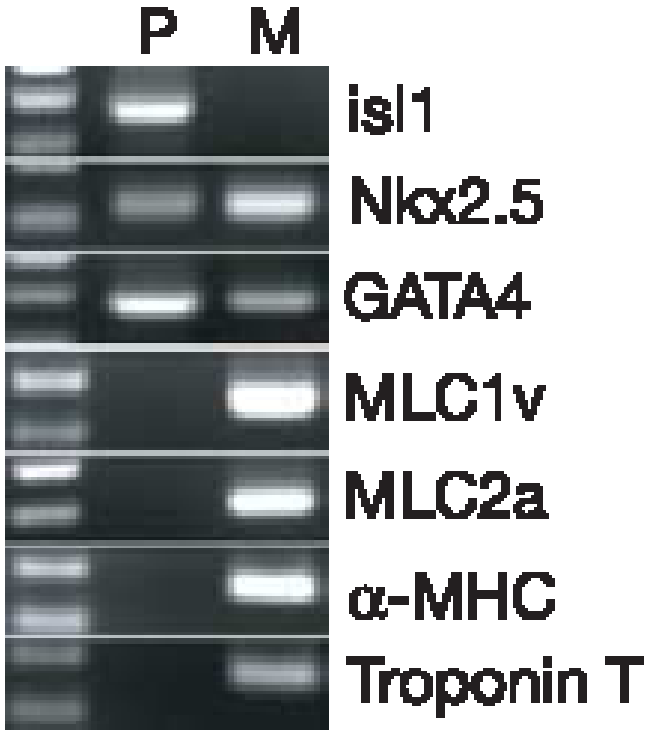
Cardiac Niches of stem Cells



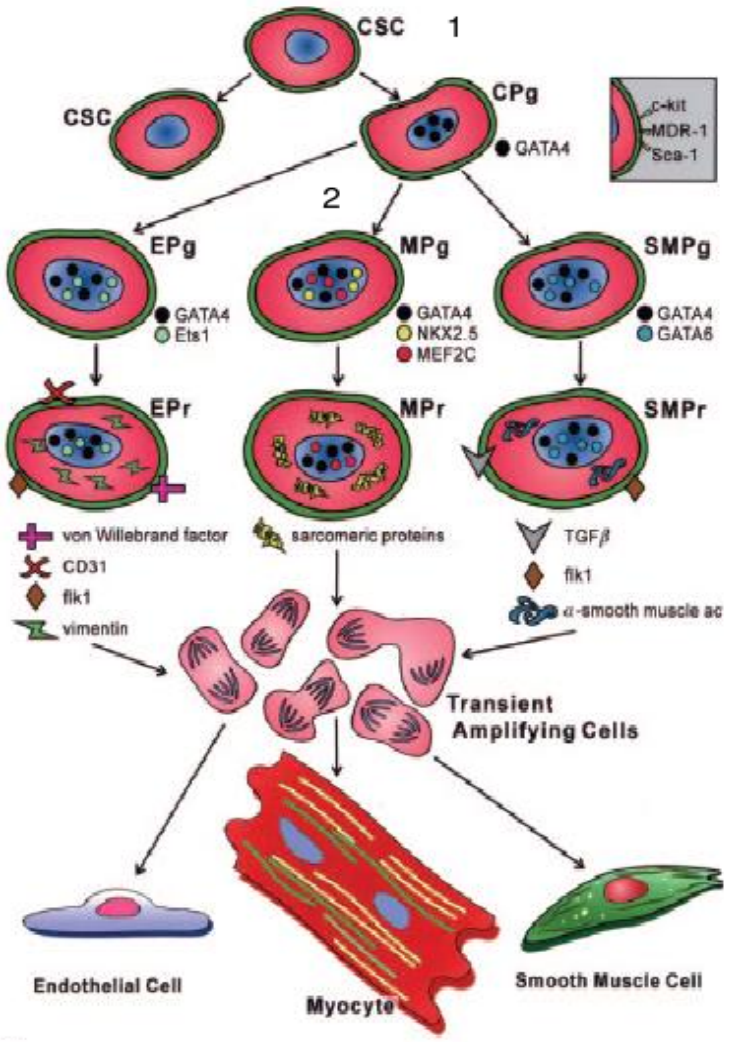


Cardiac Regeneration From Cardiomyoblasts

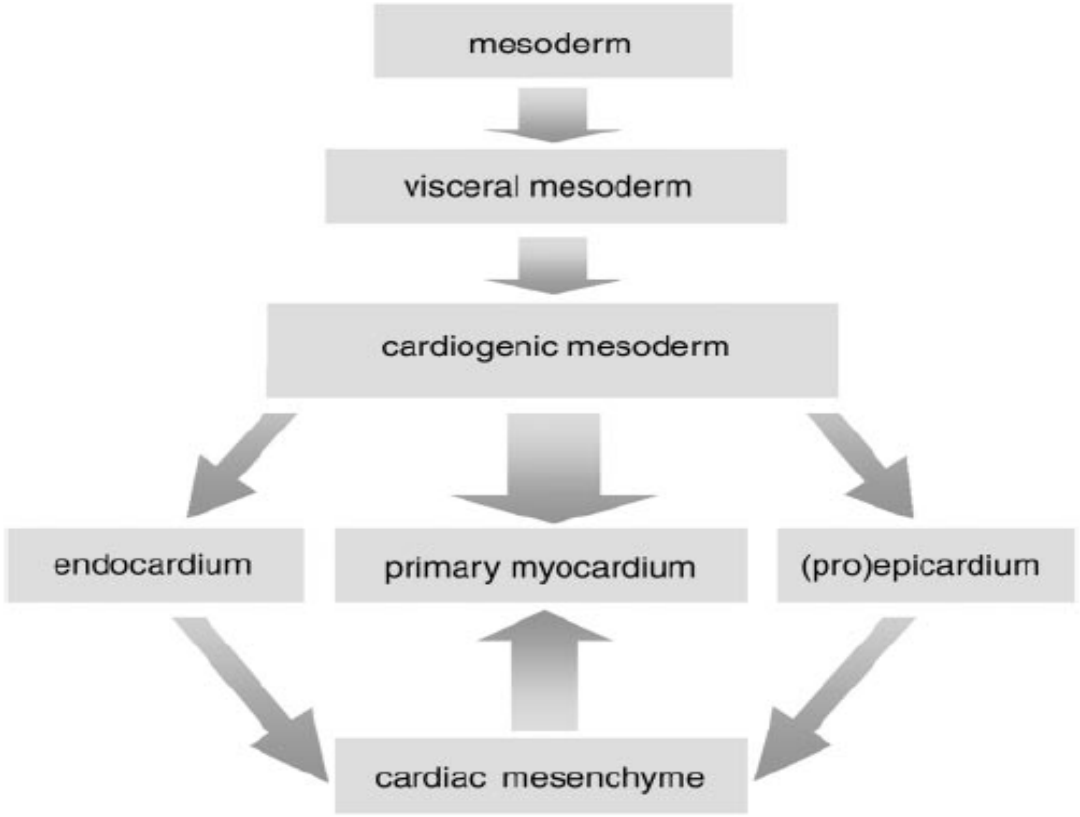




Cardiac Regeneration From Cardiomyoblasts

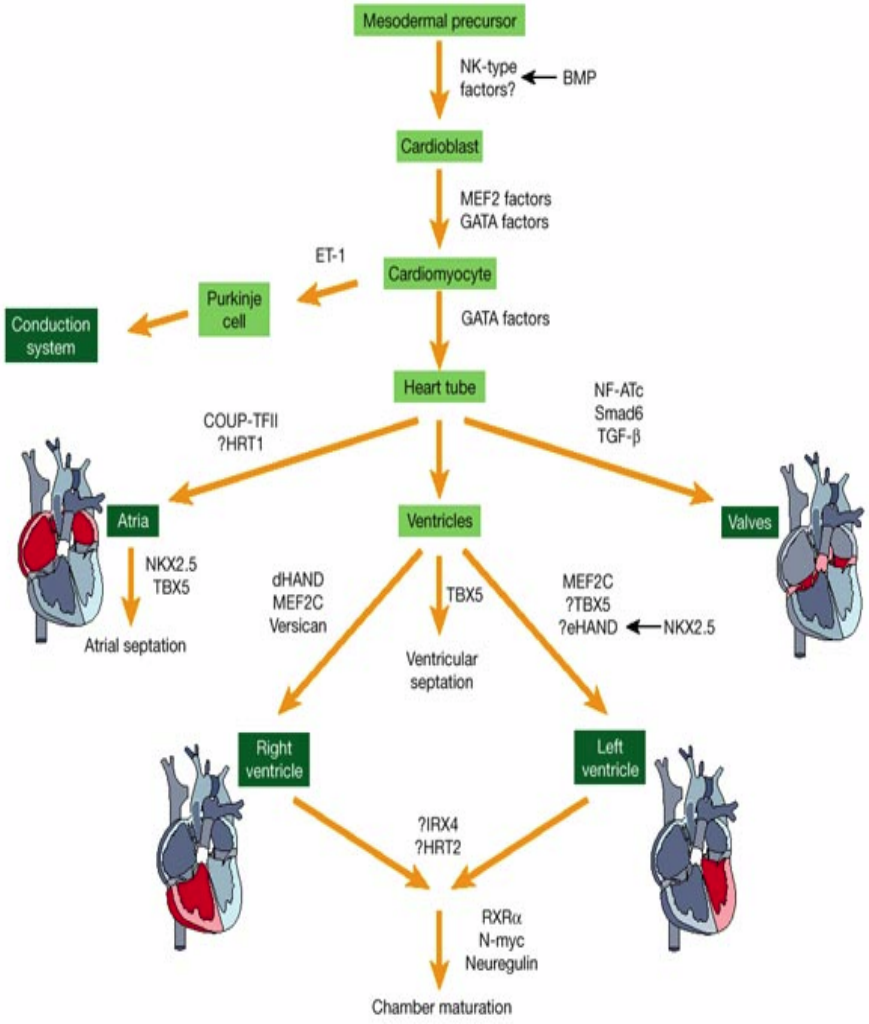


Cardiac Cell Types
Origin and Diversity

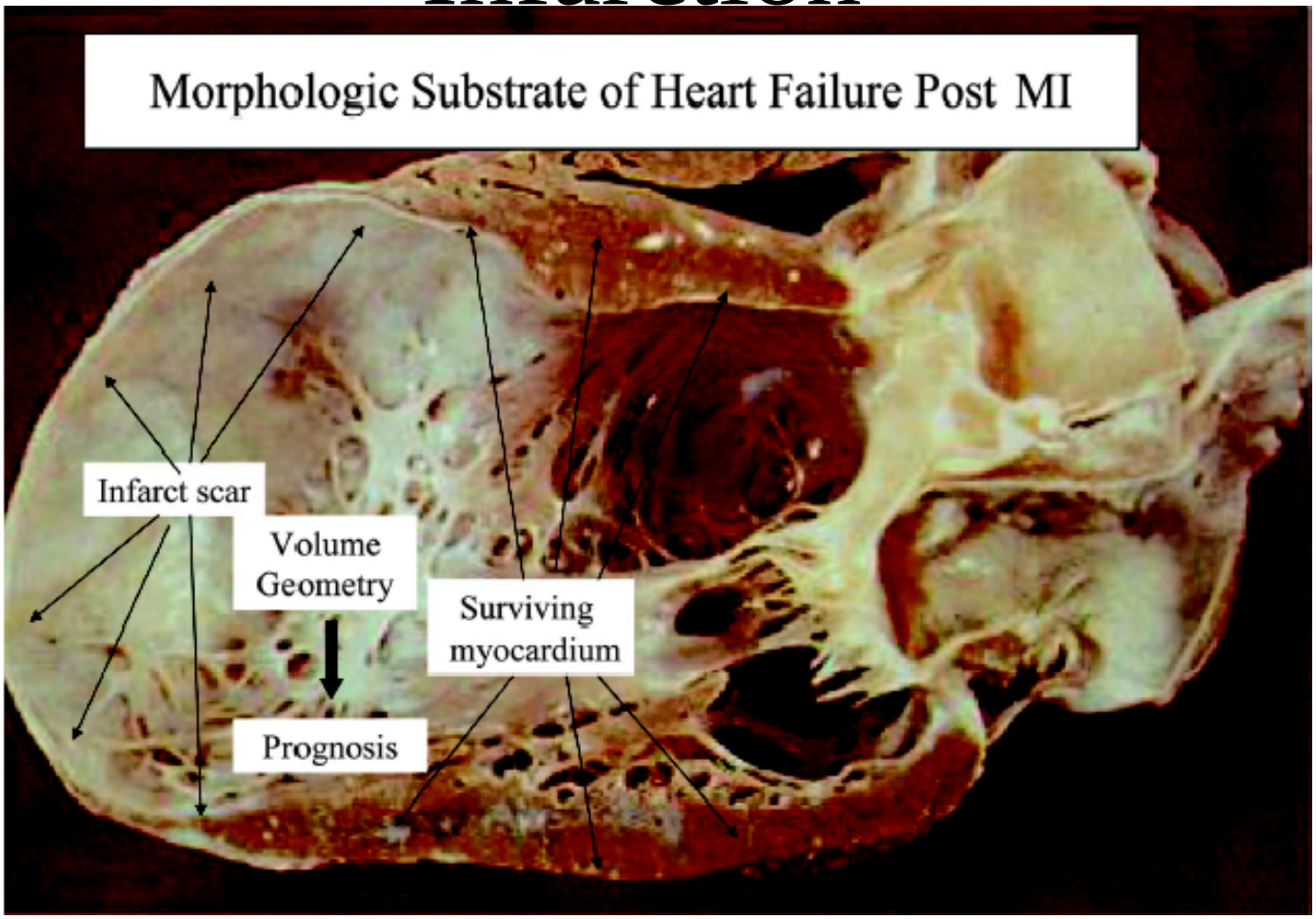


Regulation of Cardiac Progenitor Cells Proliferation and Differentiation by microRNAs

- Gene regulatory pathways in cardiac development



Wound Model of Myocardial Infarction



Myocardial Regeneration Clinical Trials

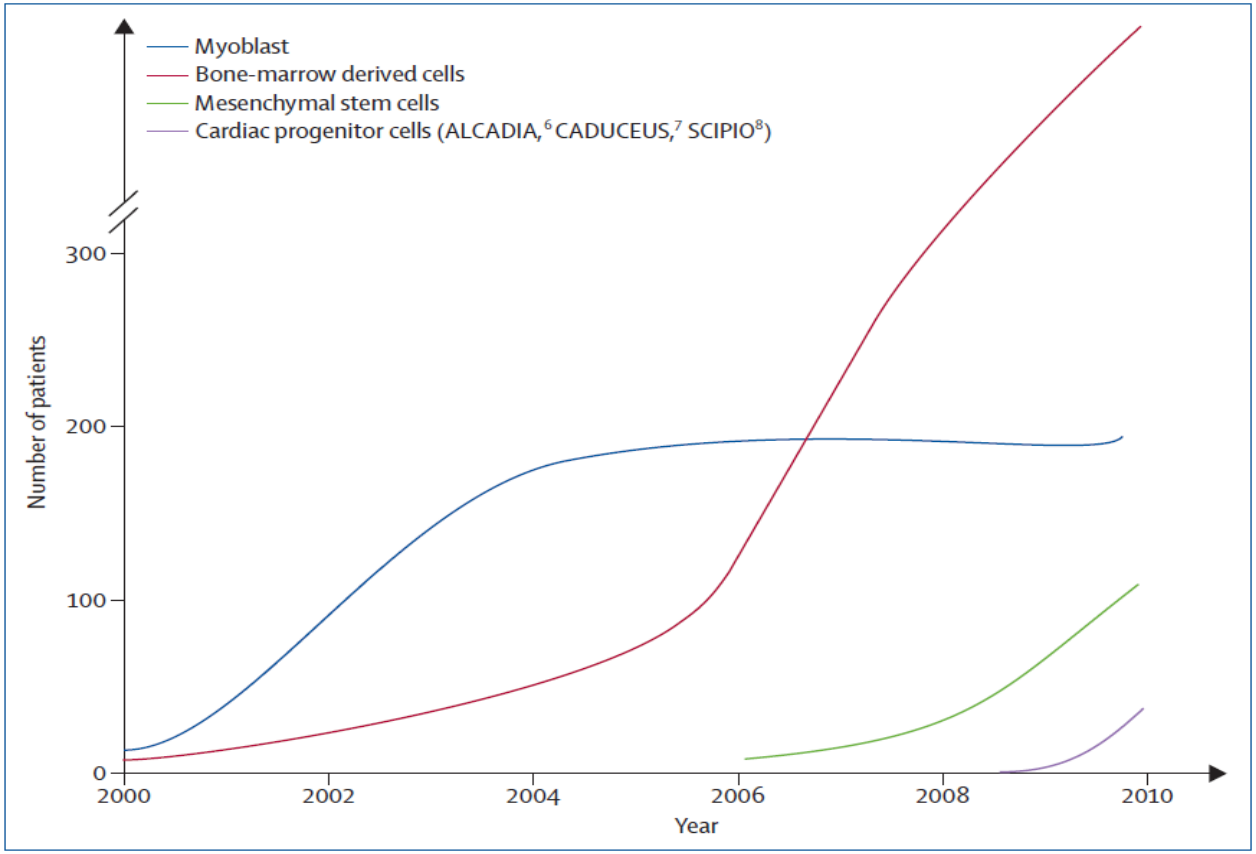
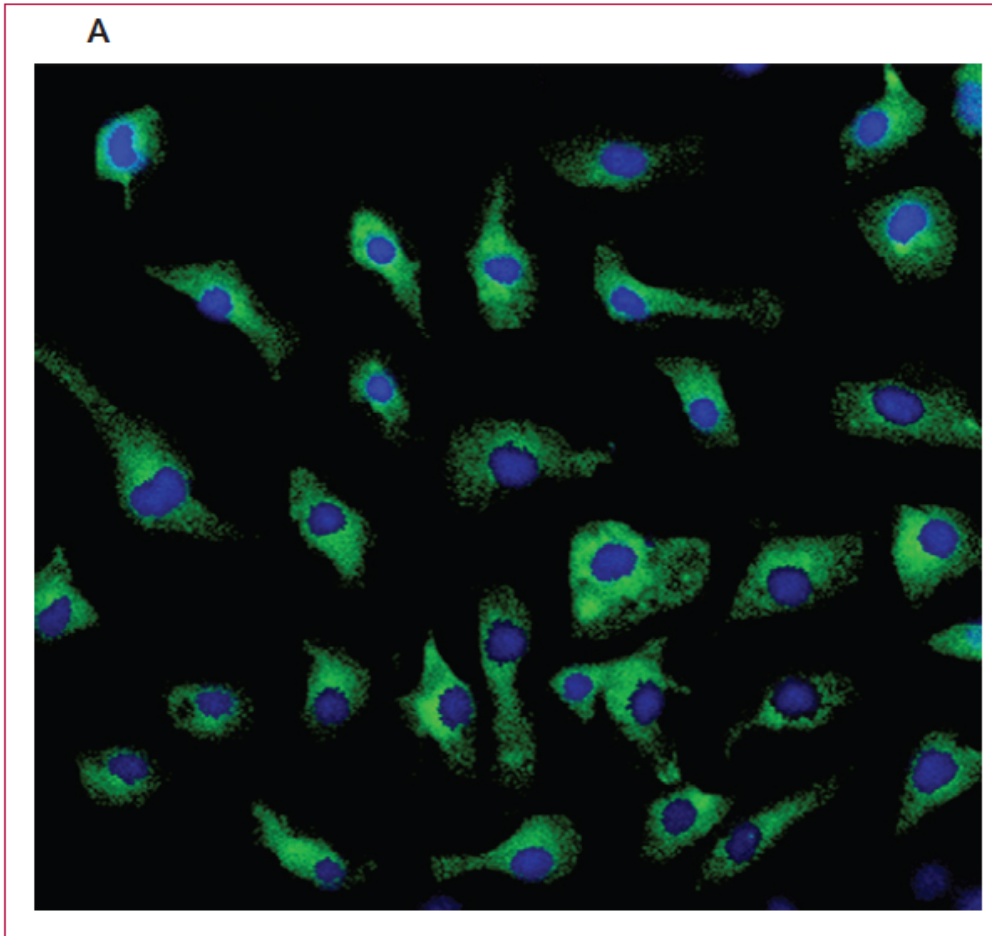


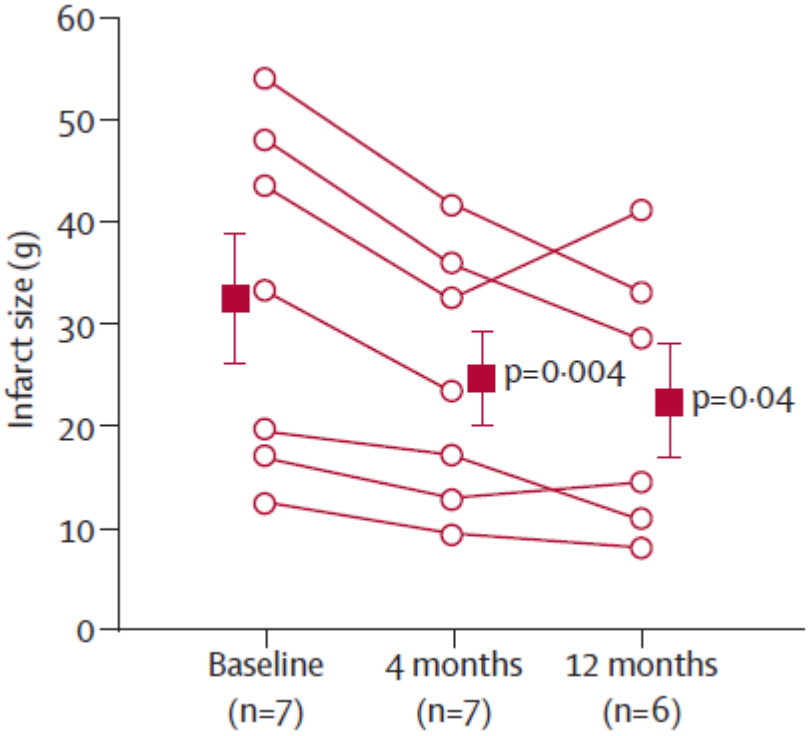
Figure: **Clinical trials of cardiac stem cell therapy**

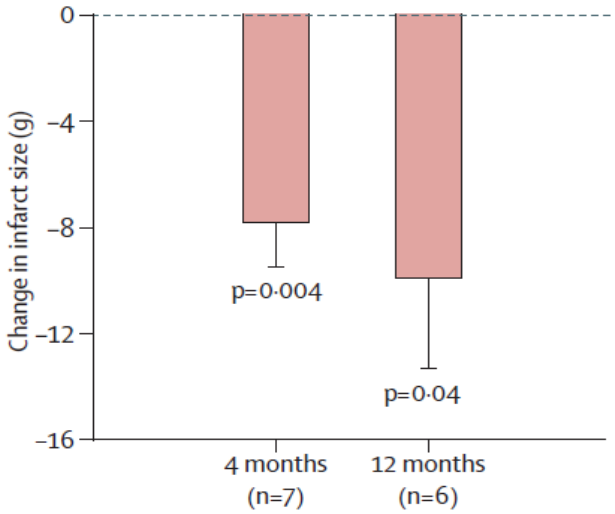
Myocardial Regeneration
CSC Clinical Trials



SCIPIO

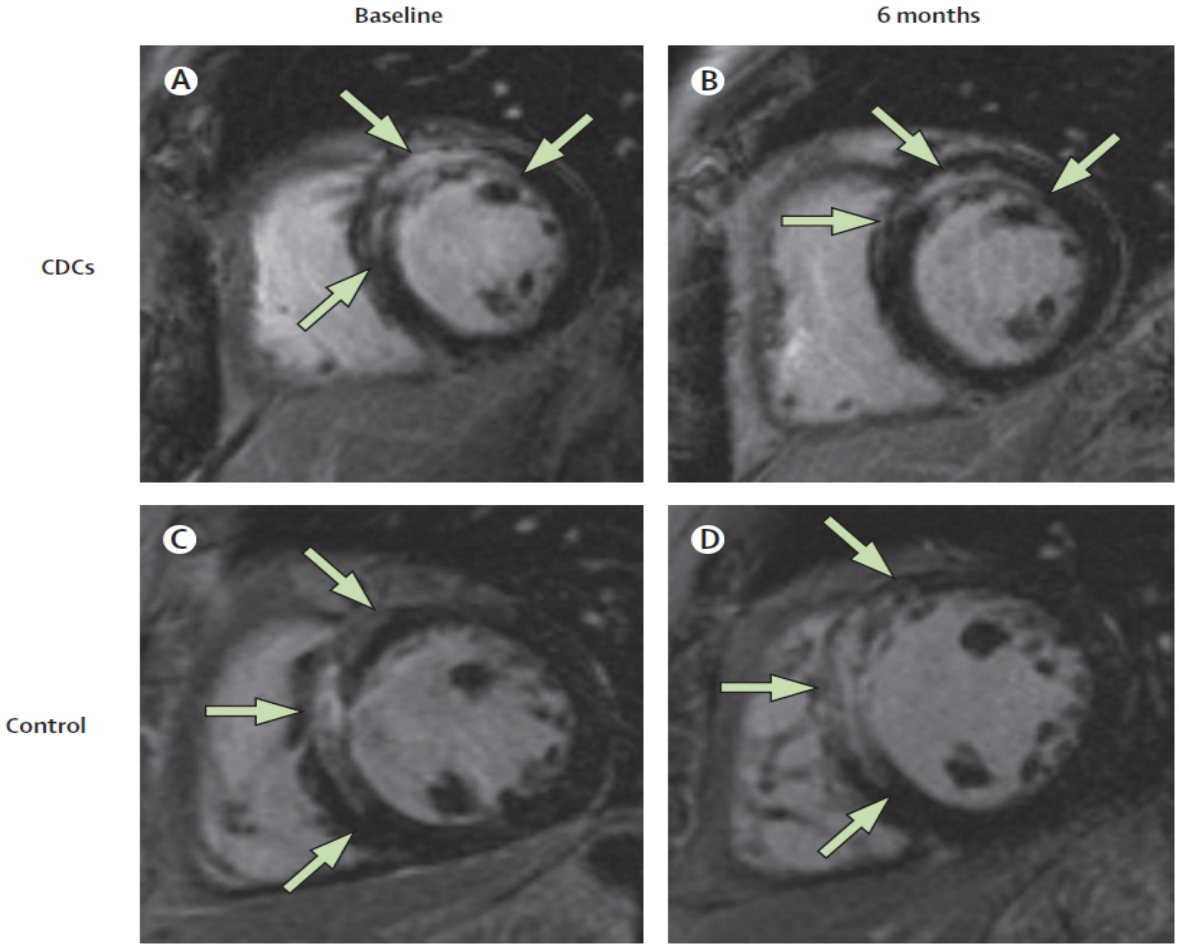
Myocardial Regeneration
CSC Clinical Trials





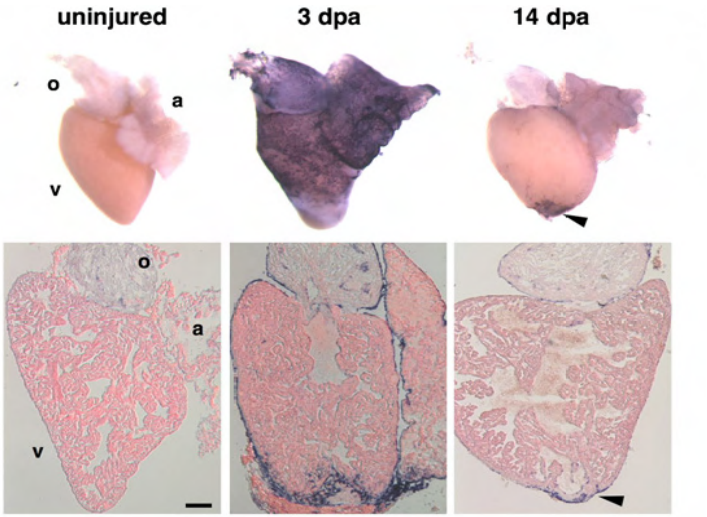
SCIPIO

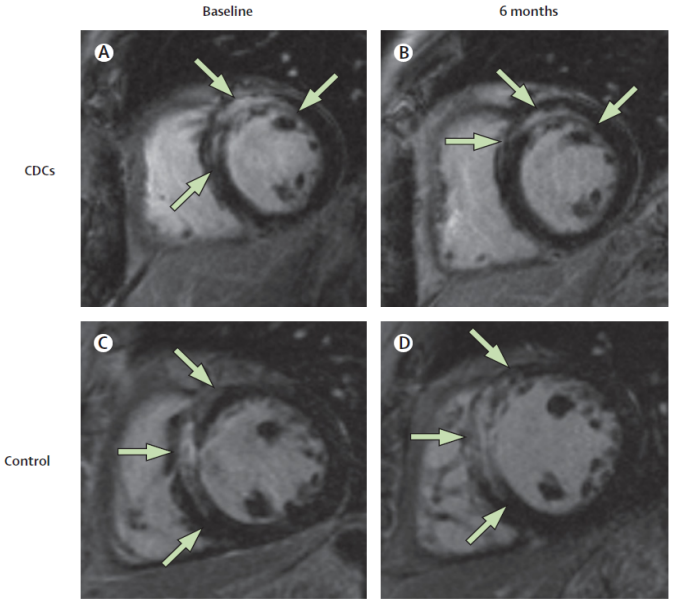
Myocardial Regeneration
CSC Clinical Trials

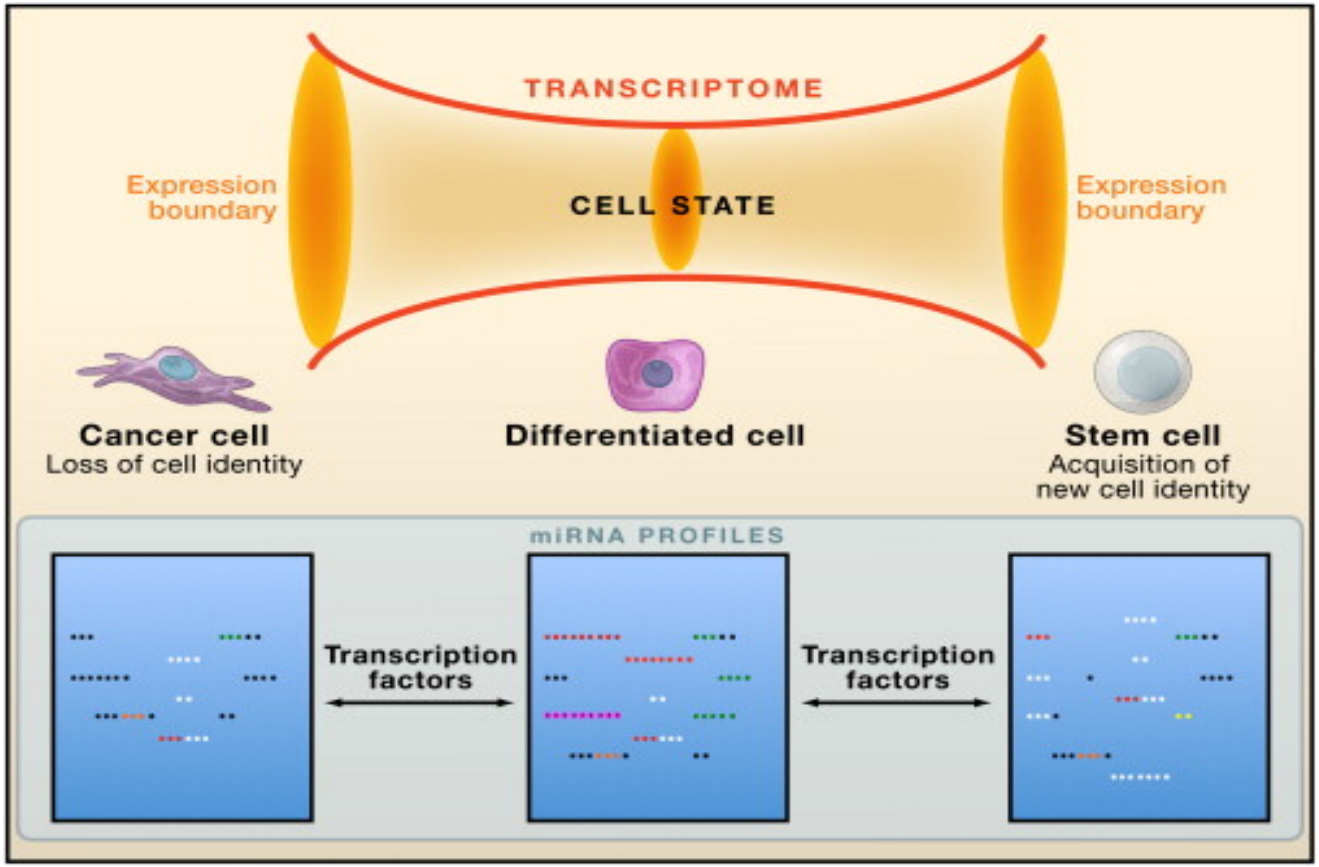


CADUCEUS

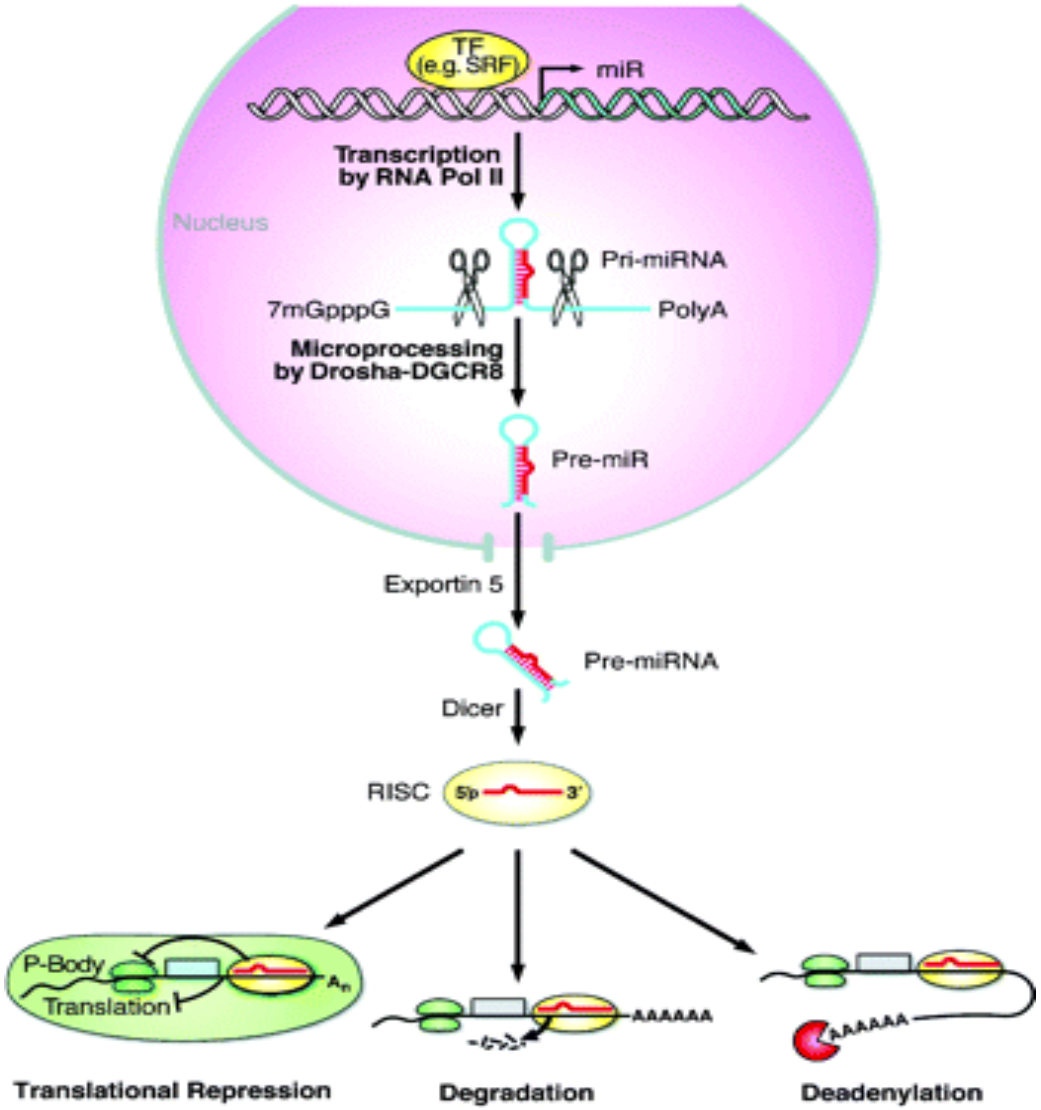
Cardiac Regeneration

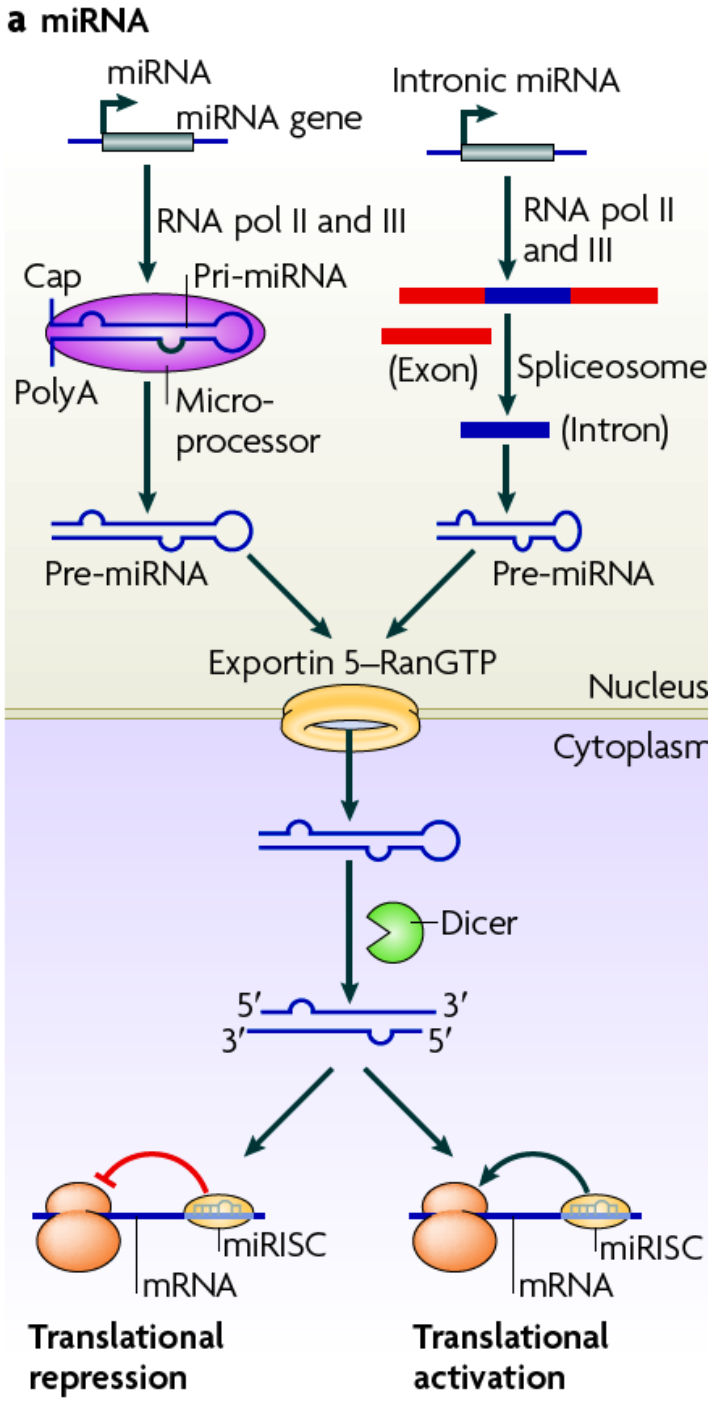





TRANSCRIPTOME
Expression boundary
CELL STATE
Expression boundary
Cancer cell
Loss of cell identity
Differentiated cell
Stem cell
Acquisition of new cell identity
miRNA PROFILES
Transcription factors
Transcription factors

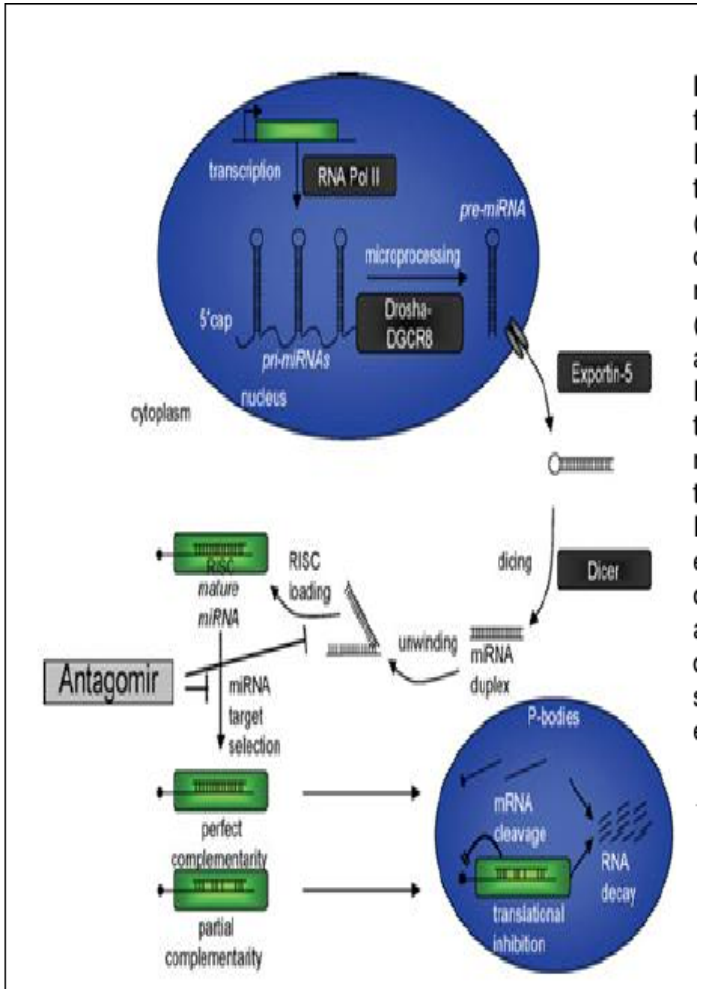
Regulation of Cardiac Progenitor Cells Proliferation and Differentiation by microRNAs



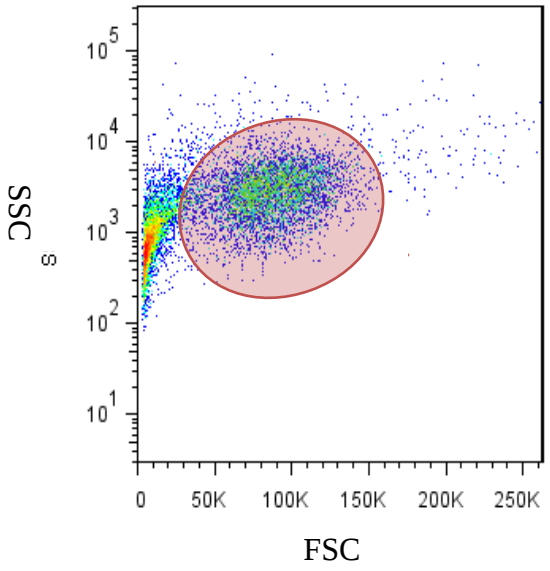

a miRNA
miRNA
miRNA gene
Intronic miRNA
RNA pol II and III
RNA pol II and III
Cap
Pri-miRNA
PolyA
Micro-processor
(Exon)
Spliceosome
(Intron)
Pre-miRNA
Pre-miRNA
Exportin 5–RanGTP
Nucleus
Cytoplasm
Dicer
5′
3′
3′
5′
miRISC
mRNA
miRISC
mRNA
Translational repression
Translational activation

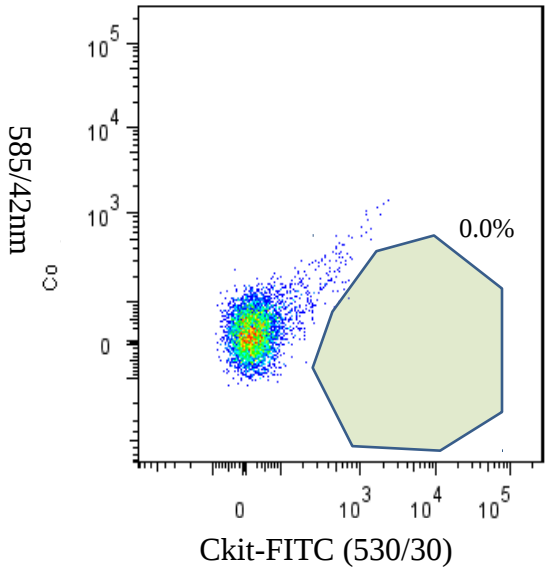
Regulation of Cardiac Progenitor Cells Proliferation and Differentiation by microRNAs

Multiple regulatory and interference targets

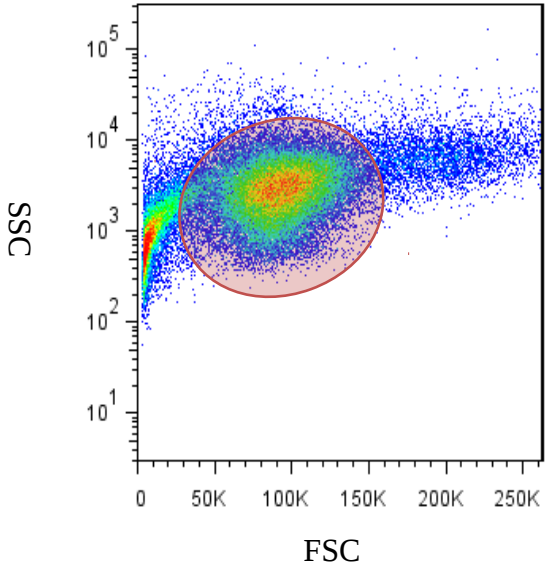


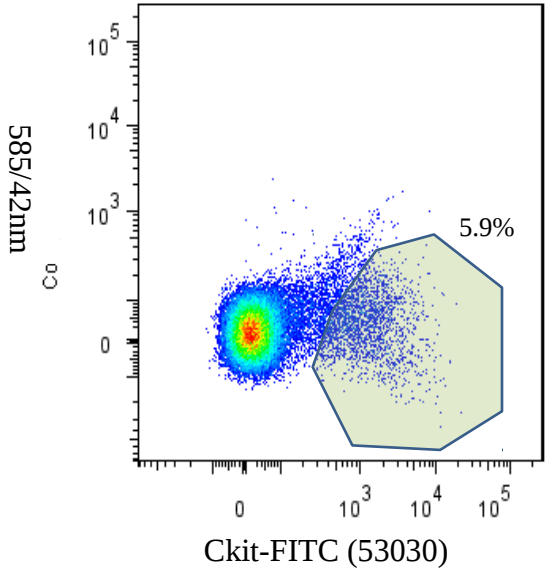
Unstained

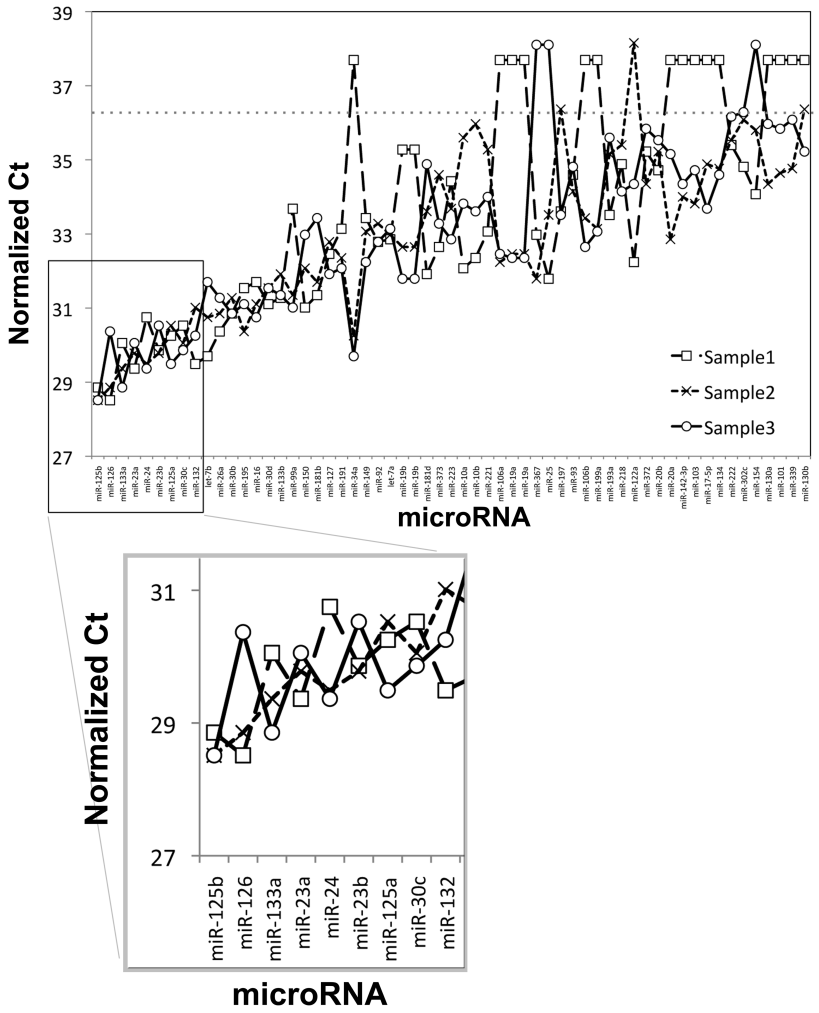


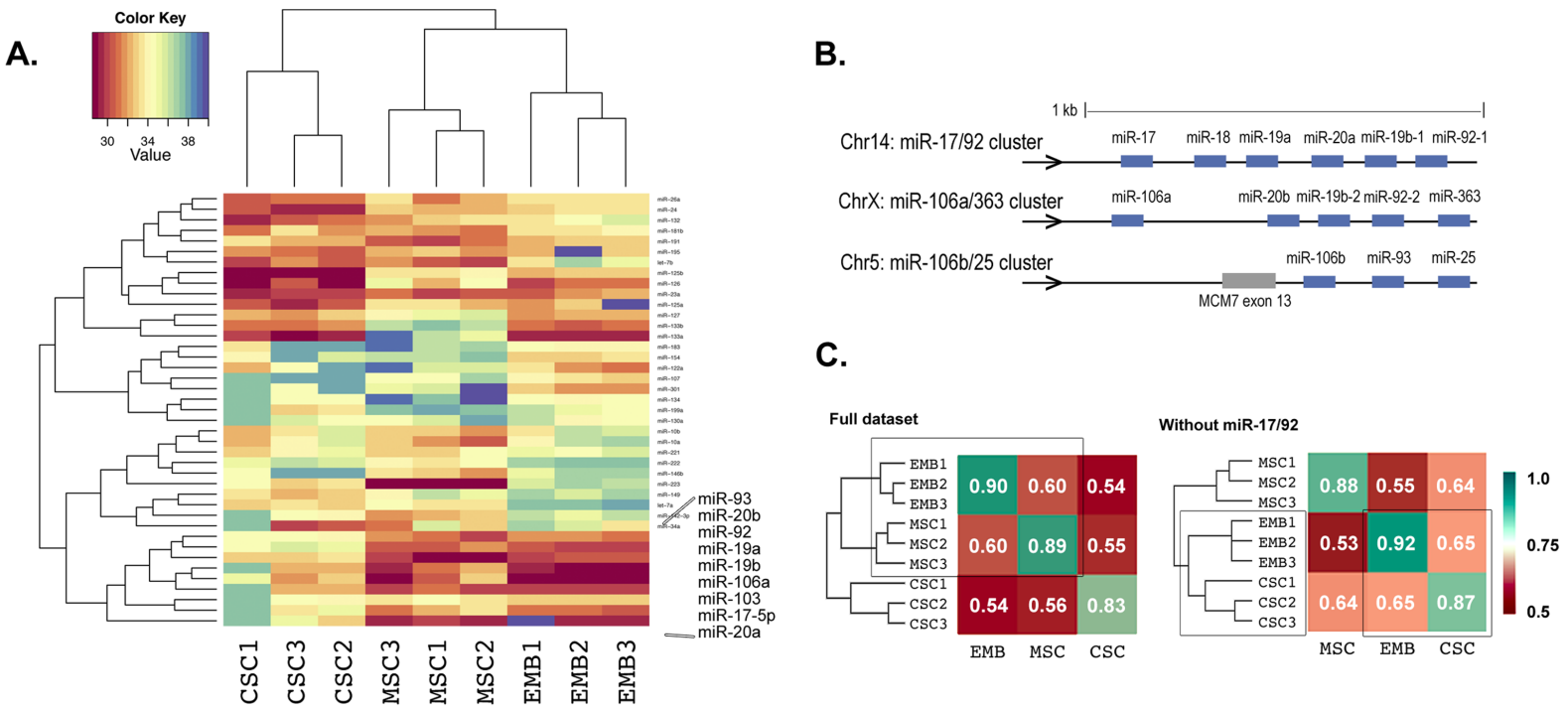


sca1-FITC

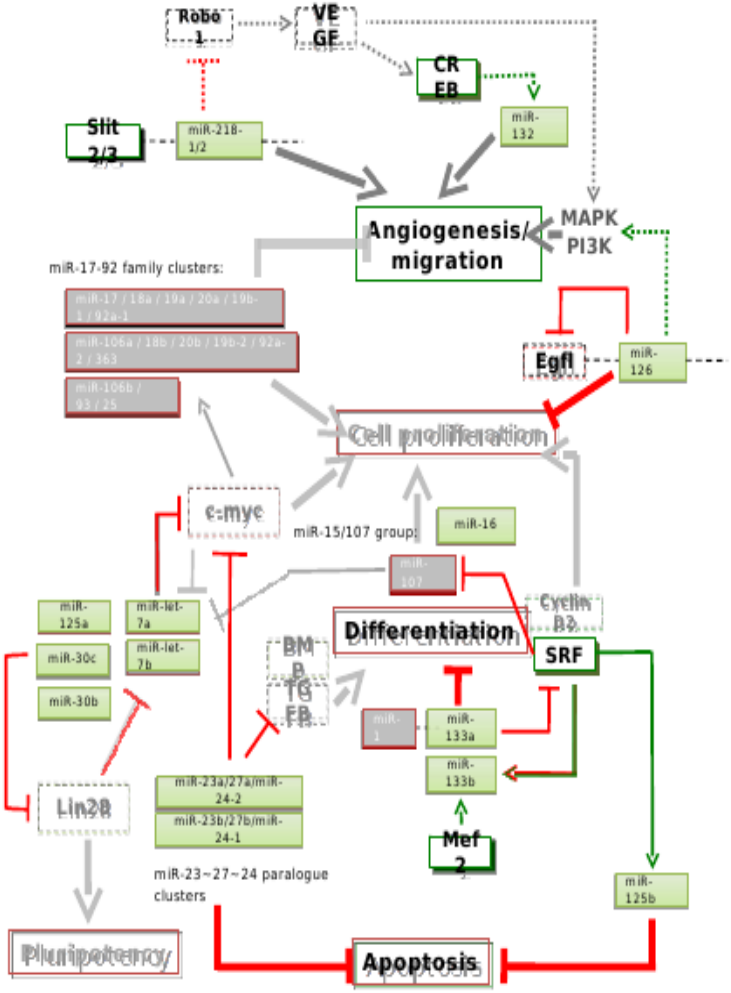




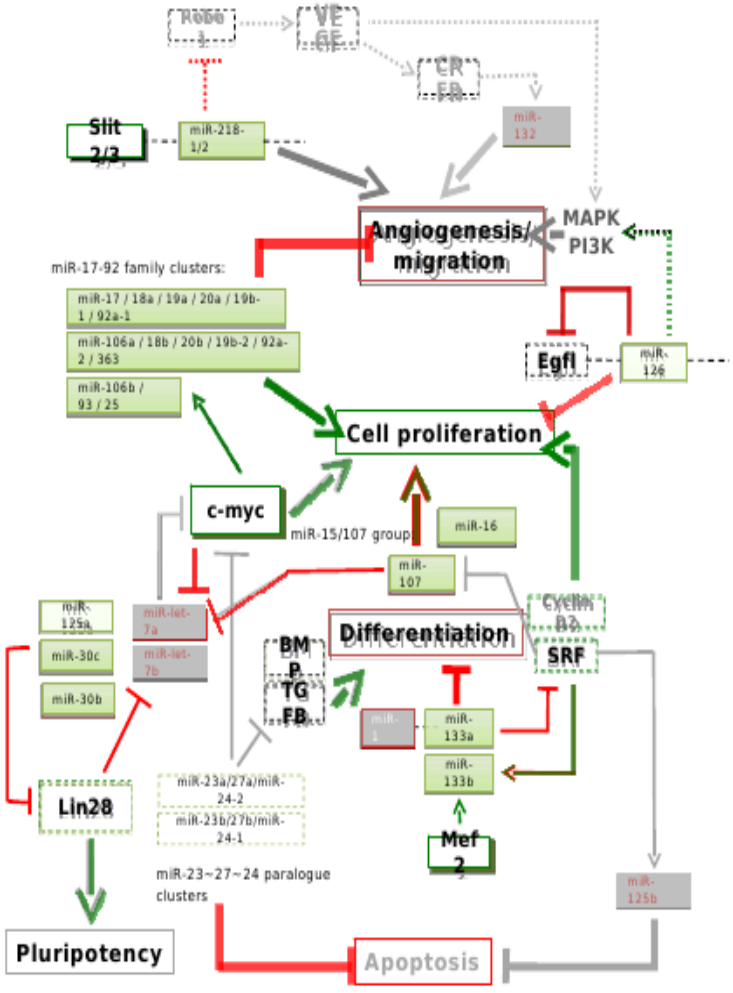

Normalized Ct
39
37
35
33
31
29
27
Sample1
Sample2
Sample3
microRNA
Normalized Ct
31
29
27
miR-125b
miR-126
miR-133a
miR-23a
miR-24
miR-23b
miR-125a
miR-30c
miR-132
microRNA

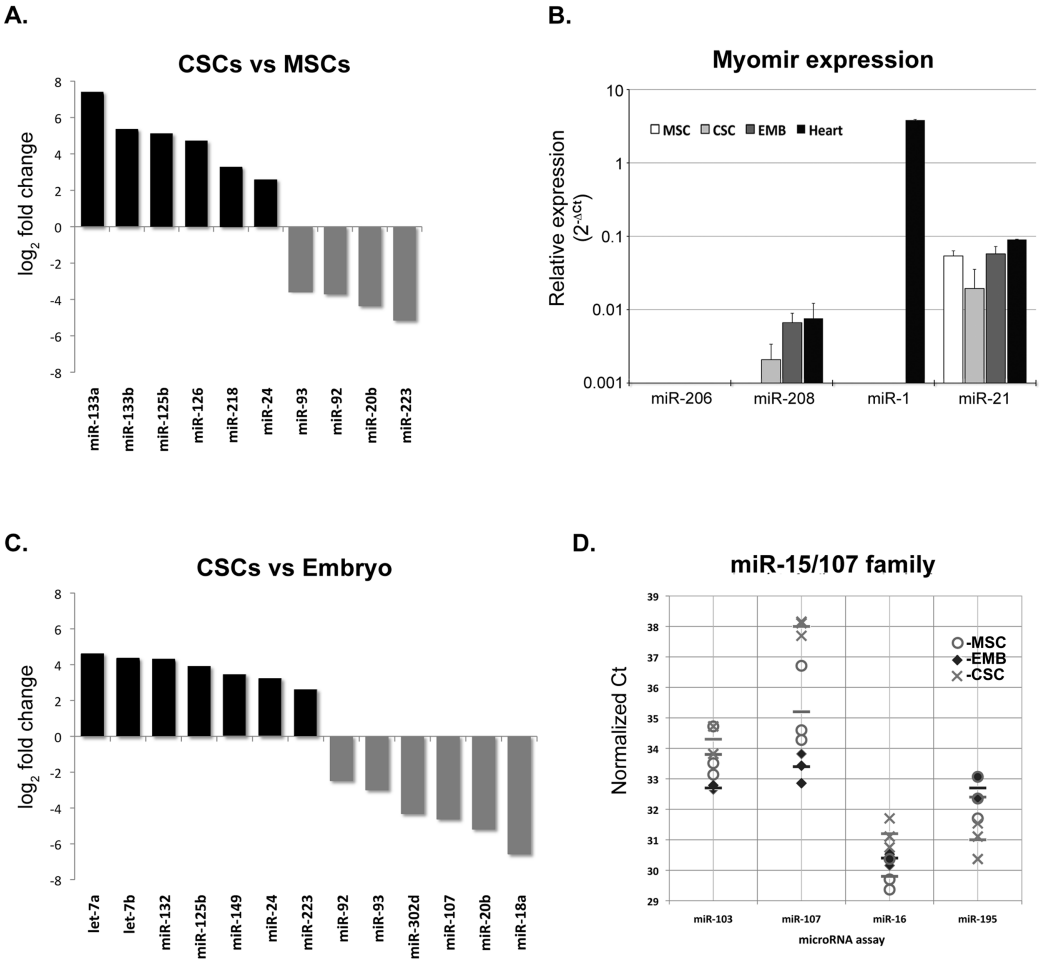

A.
Color Key
30
34
38
Value
miR-93
miR-20b
miR-92
miR-19a
miR-19b
miR-106a
miR-103
miR-17-5p
miR-20a
CSC1
CSC3
CSC2
MSC3
MSC1
MSC2
EMB1
EMB2
EMB3
B.
1 kb
Chr14: miR-17/92 cluster
miR-17
miR-18
miR-19a
miR-20a
miR-19b-1
miR-92-1
ChrX: miR-106a/363 cluster
miR-106a
miR-20b
miR-19b-2
miR-92-2
miR-363
Chr5: miR-106b/25 cluster
miR-106b
miR-93
miR-25
MCM7 exon 13
C.
Full dataset
EMB1
EMB2
EMB3
MSC1
MSC2
MSC3
CSC1
CSC2
CSC3
0.90
0.60
0.54
0.60
0.89
0.55
0.54
0.56
0.83
EMB
MSC
CSC
Without miR-17/92
MSC1
MSC2
MSC3
EMB1
EMB2
EMB3
CSC1
CSC2
CSC3
0.88
0.55
0.64
0.53
0.92
0.65
0.64
0.65
0.87
MSC
EMB
CSC
1.0
0.75
0.5

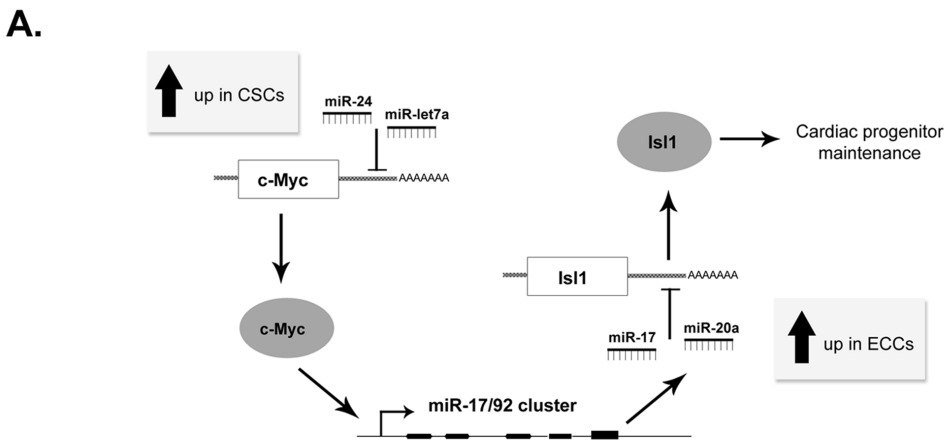
Cardiac stem cells

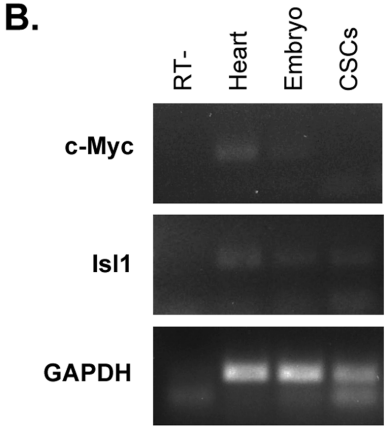


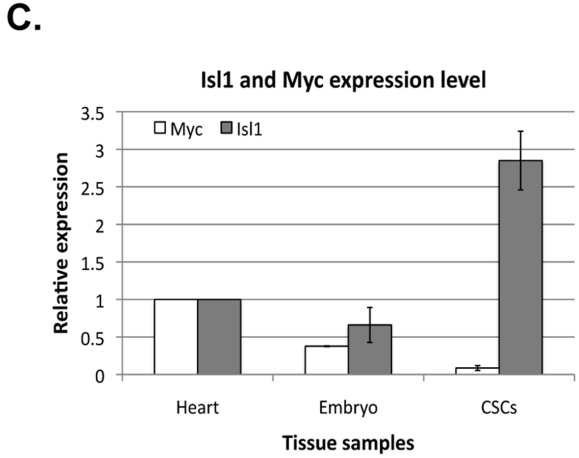
E9 embryo heart

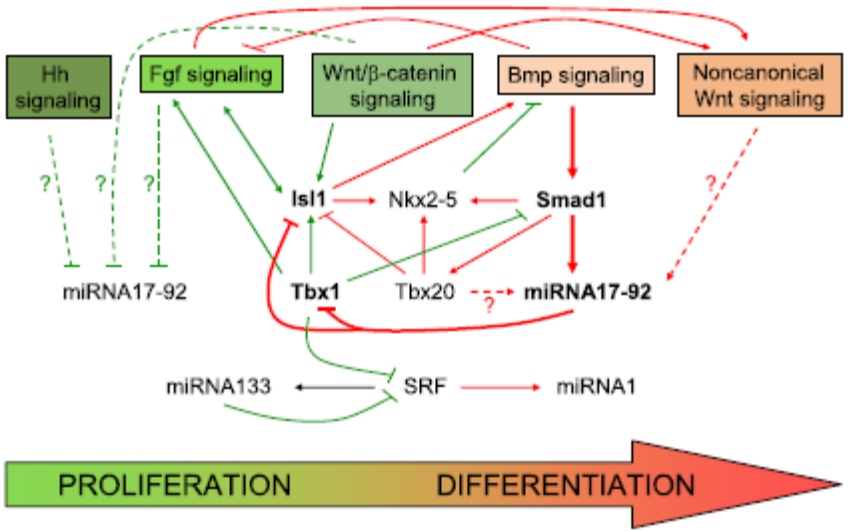


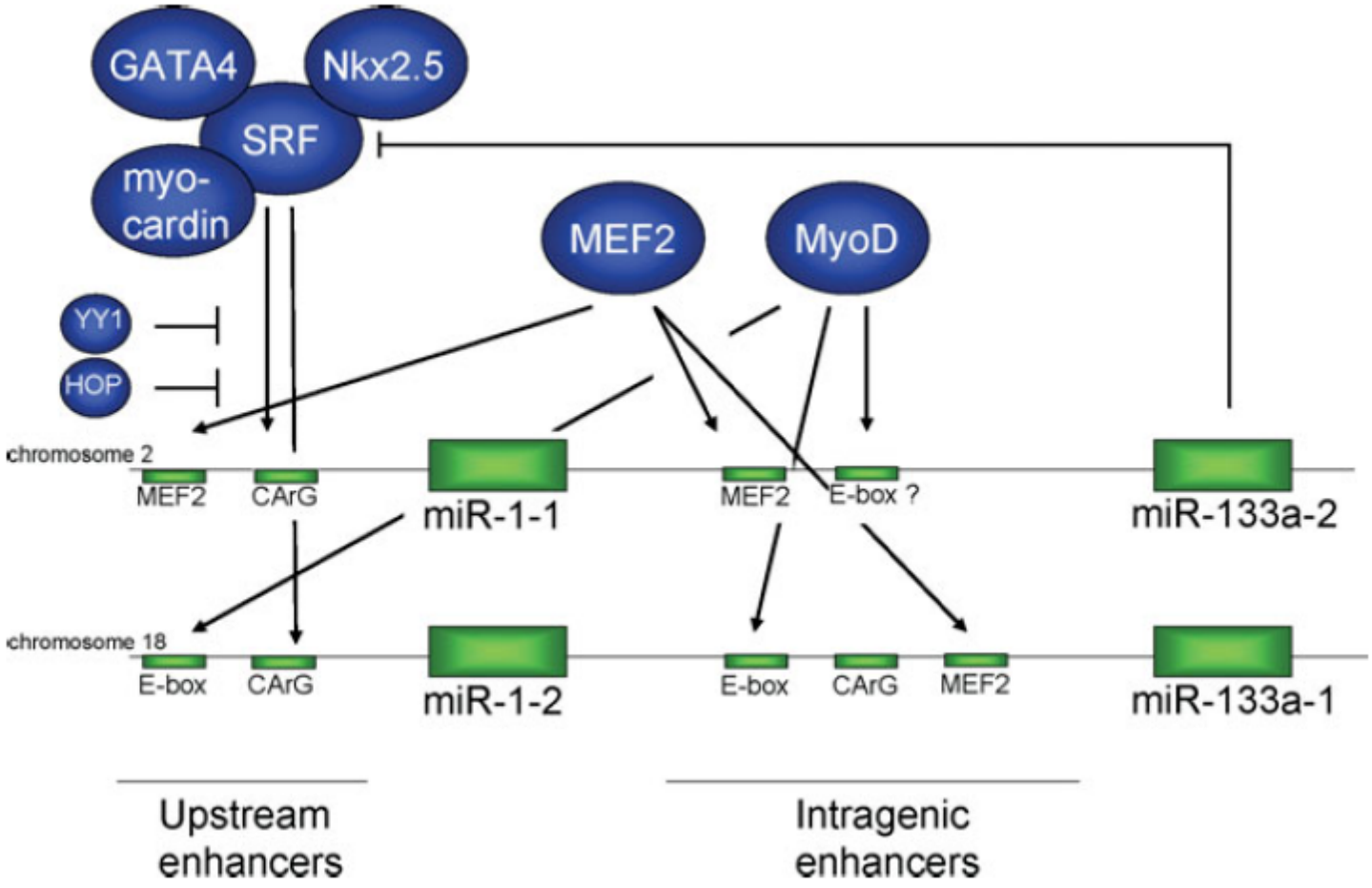

A.
CSCs vs MSCs
log2 fold change
8
6
4
2
0
-2
-4
-6
-8
miR-133a
miR-133b
miR-125b
miR-126
miR-218
miR-24
miR-93
miR-92
miR-20b
miR-223
B.
Myomir expression
Relative expression (2-ΔCt)
10
1
0.1
0.01
0.001
MSC
CSC
EMB
Heart
miR-206
miR-208
miR-1
miR-21
C.
CSCs vs Embryo
log2 fold change
8
6
4
2
0
-2
-4
-6
-8
let-7a
let-7b
miR-132
miR-125b
miR-149
miR-24
miR-223
miR-92
miR-93
miR-302d
miR-107
miR-20b
miR-18a
D.
miR-15/107 family
Normalized Ct
39
38
37
36
35
34
33
32
31
30
29
-MSC
-EMB
-CSC
miR-103
miR-107
miR-16
miR-195
microRNA assay

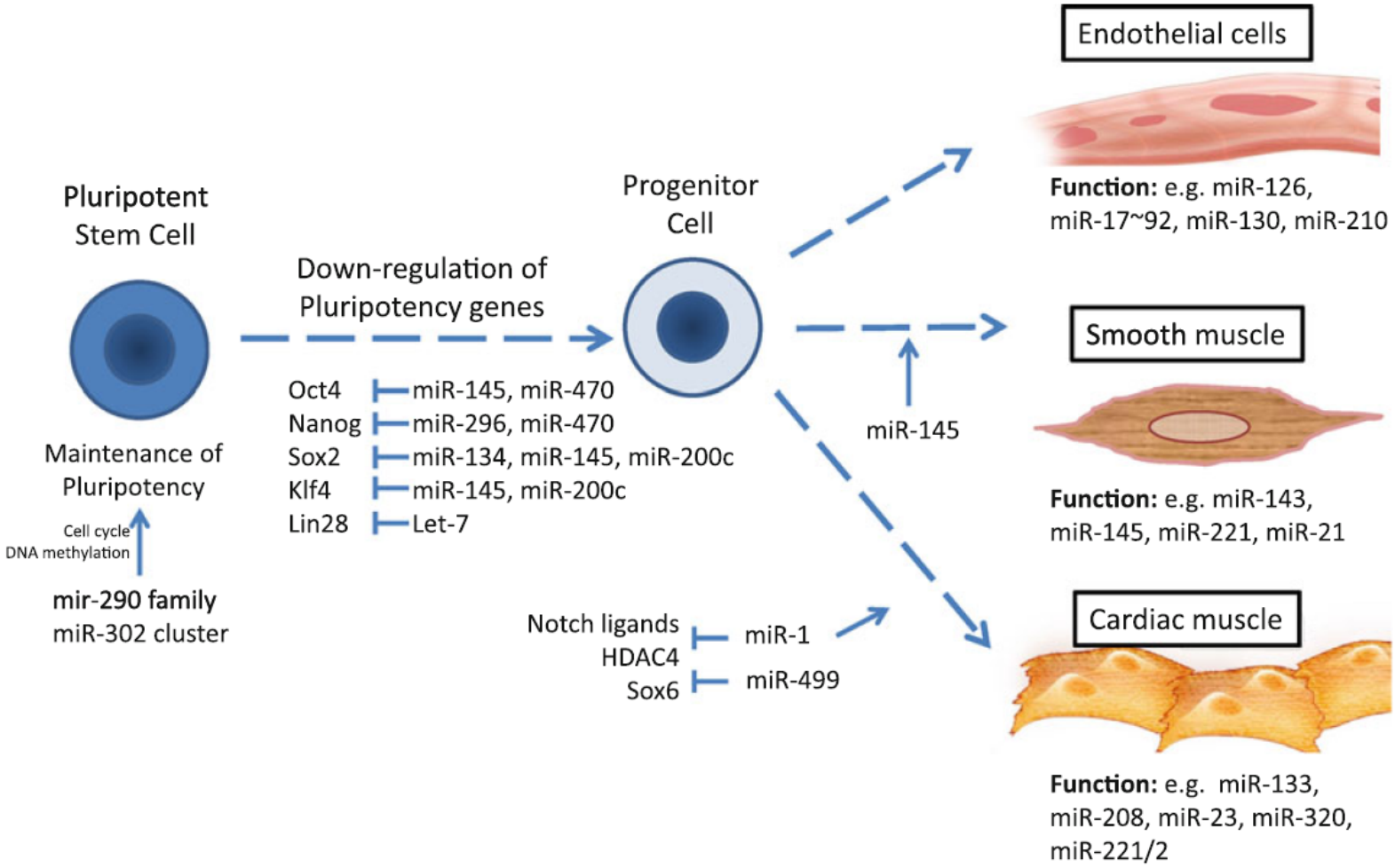

A.
up in CSCs
miR-24
miR-let7a
c-Myc
AAAAAAA
c-Myc
miR-17/92 cluster
Isl1
Cardiac progenitor maintenance
Isl1
AAAAAAA
miR-17
miR-20a
up in ECCs


B.
RT-
Heart
Embryo
CSCs
c-Myc
Isl1
GAPDH

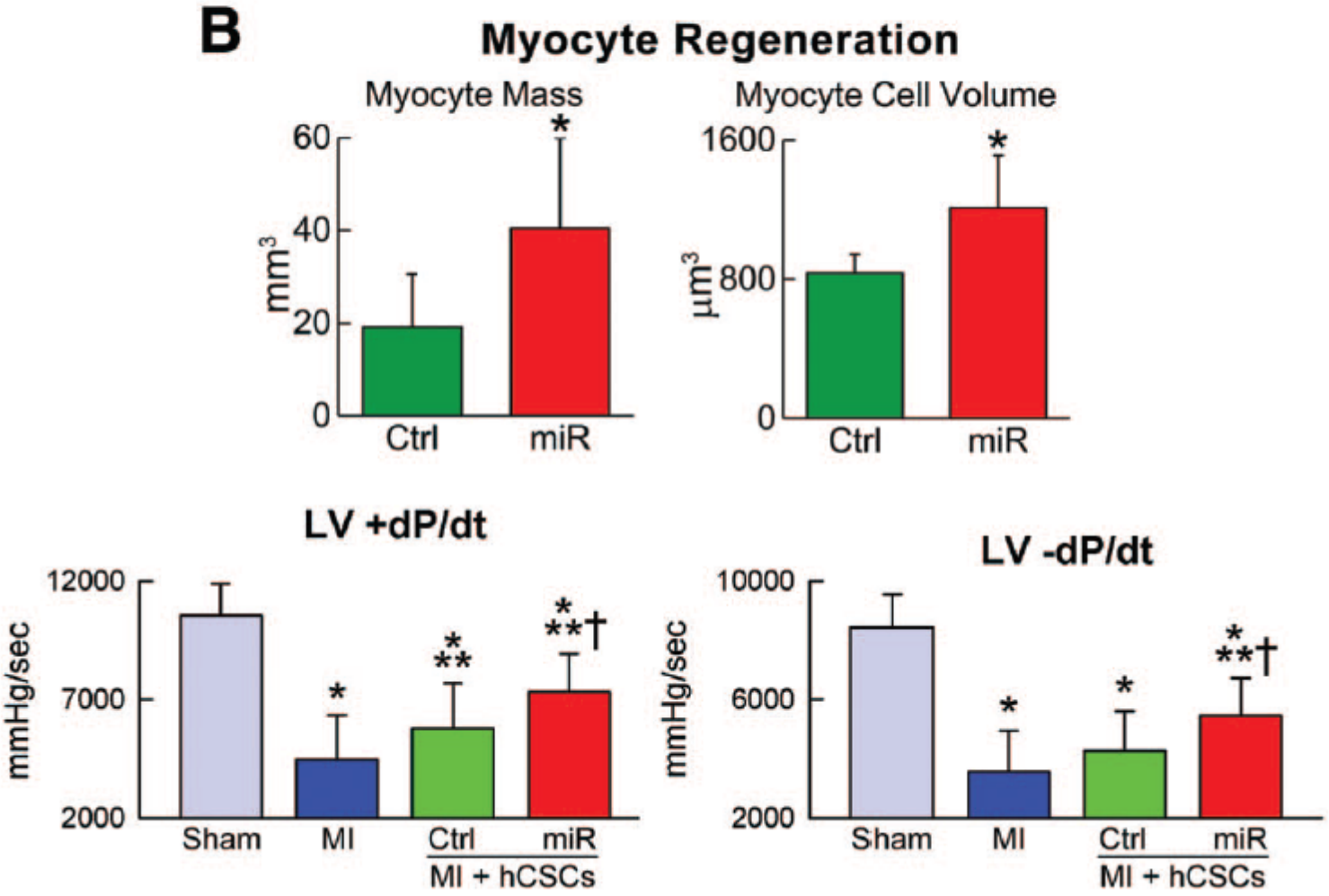

C.
Isl1 and Myc expression level
Myc
Isl1
Relative expression
3.5
3
2.5
2
1.5
1
0.5
0
Heart
Embryo
CSCs
Tissue samples

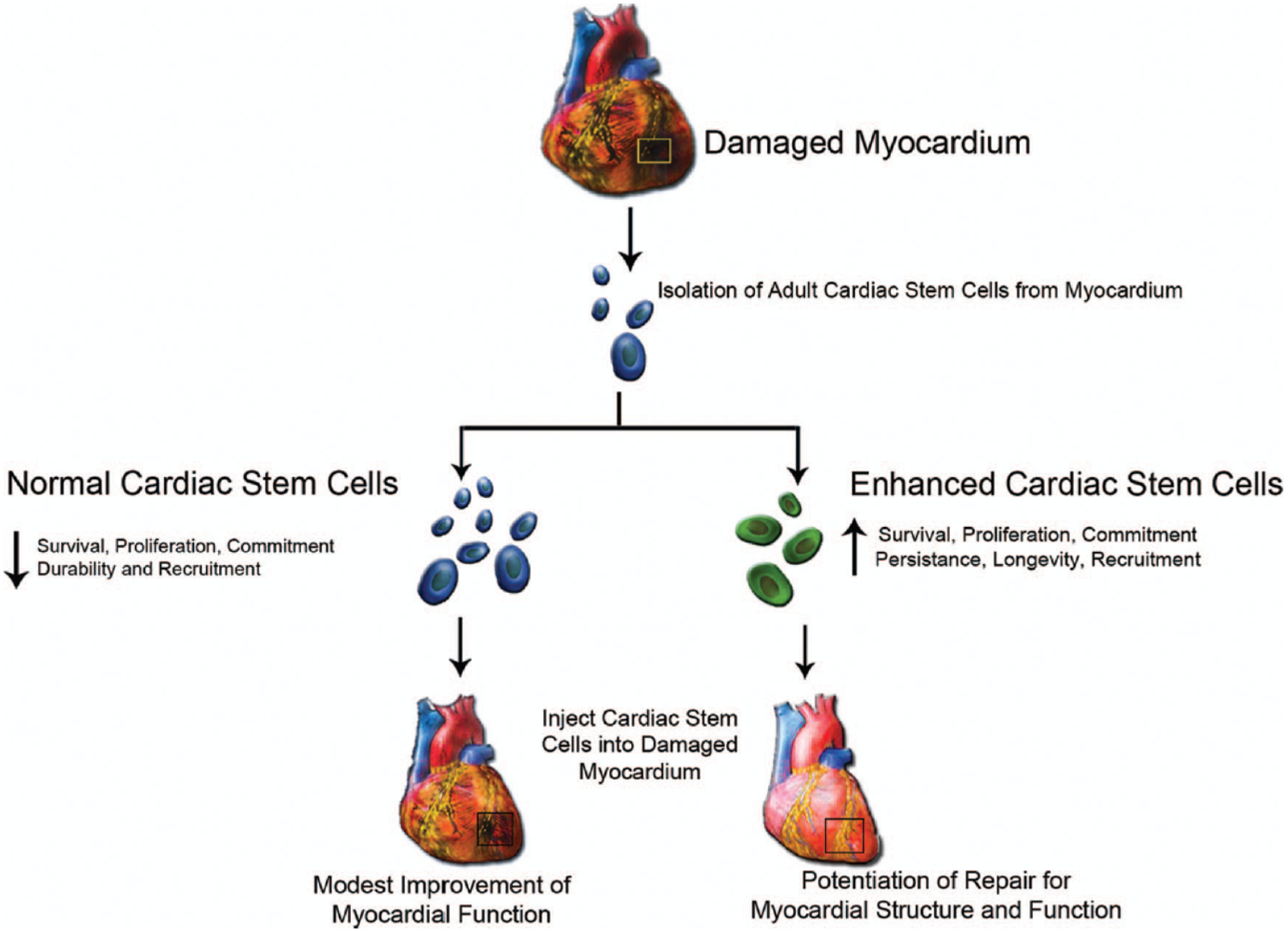

Hh signaling
Fgf signaling
Wnt/β-catenin signaling
Bmp signaling
Noncanonical Wnt signaling
?
?
?
?
Isl1
Nkx2-5
Smad1
miRNA17-92
Tbx1
Tbx20
?
miRNA17-92
miRNA133
SRF
miRNA1
PROLIFERATION
DIFFERENTIATION


GATA4
Nkx2.5
SRF
myo-
cardin
MEF2
MyoD
YY1
HOP
chromosome 2
MEF2
CArG
miR-1-1
MEF2
E-box ?
miR-133a-2
chromosome 18
E-box
CArG
miR-1-2
E-box
CArG
MEF2
miR-133a-1
Upstream
enhancers
Intragenic
enhancers


Pluripotent Stem Cell
Maintenance of Pluripotency
Cell cycle
DNA methylation
mir-290 family
miR-302 cluster
Down-regulation of Pluripotency genes
Oct4 ⊣ miR-145, miR-470
Nanog ⊣ miR-296, miR-470
Sox2 ⊣ miR-134, miR-145, miR-200c
Klf4 ⊣ miR-145, miR-200c
Lin28 ⊣ Let-7
Progenitor Cell
miR-145
Notch ligands ⊣ miR-1
HDAC4
Sox6 ⊣ miR-499
Endothelial cells
Function: e.g. miR-126, miR-17~92, miR-130, miR-210
Smooth muscle
Function: e.g. miR-143, miR-145, miR-221, miR-21
Cardiac muscle
Function: e.g. miR-133, miR-208, miR-23, miR-320, miR-221/2

miR 499


B
Myocyte Regeneration
Myocyte Mass
mm3
60
40
20
0
Ctrl
miR
Myocyte Cell Volume
µm3
1600
800
0
Ctrl
miR
LV +dP/dt
mmHg/sec
12000
7000
2000
Sham
MI
Ctrl
miR
MI + hCSCs
LV -dP/dt
mmHg/sec
10000
6000
2000
Sham
MI
Ctrl
miR
MI + hCSCs


Damaged Myocardium
Isolation of Adult Cardiac Stem Cells from Myocardium
Normal Cardiac Stem Cells
Survival, Proliferation, Commitment
Durability and Recruitment
Enhanced Cardiac Stem Cells
Survival, Proliferation, Commitment
Persistance, Longevity, Recruitment
Inject Cardiac Stem
Cells into Damaged
Myocardium
Modest Improvement of
Myocardial Function
Potentiation of Repair for
Myocardial Structure and Function

. CSC display miR regulatory networks of the three cardiac lineages, eg cardiomyocyte, endothelial cels and vascular smooth muscle

. CSC overexpress anti proliferative miRs

. CSC express miRs involved in cardiac stress response