the world of (noncoding) RNA

microRNA expression

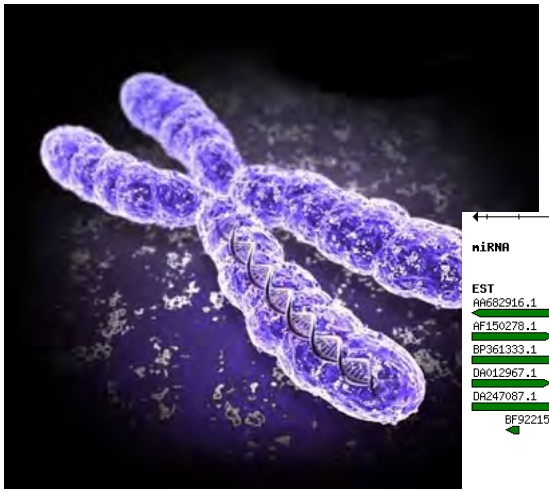
microRNA regulation

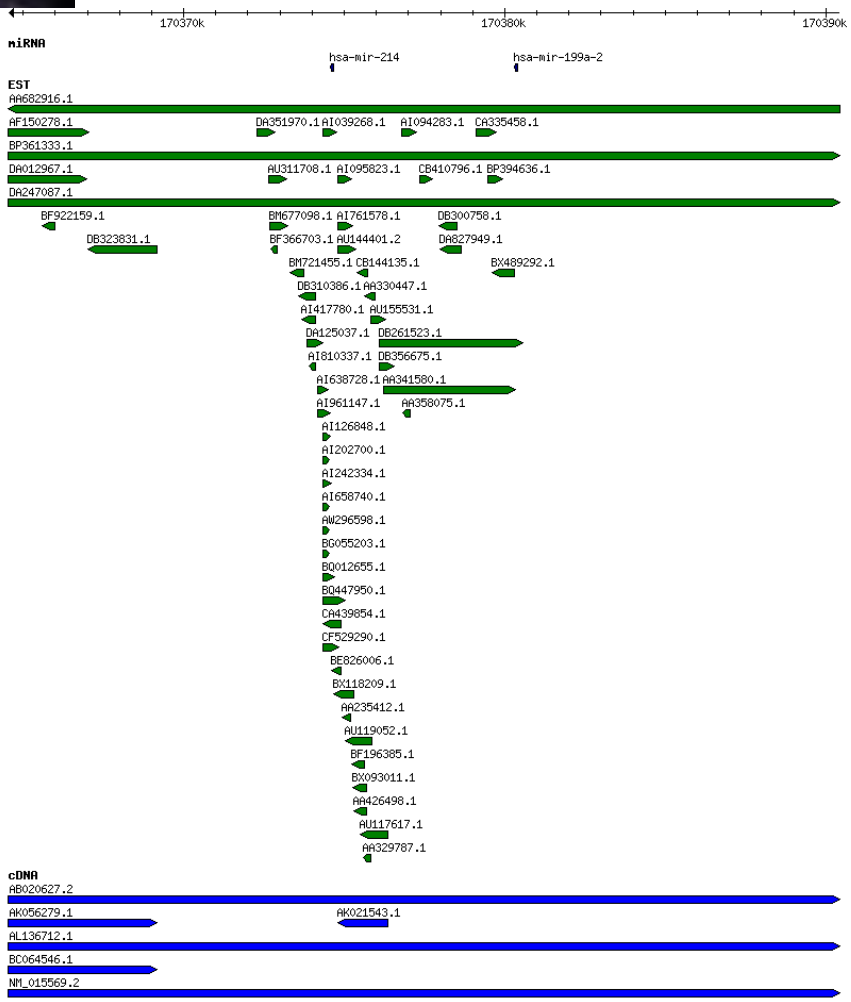
microRNA function

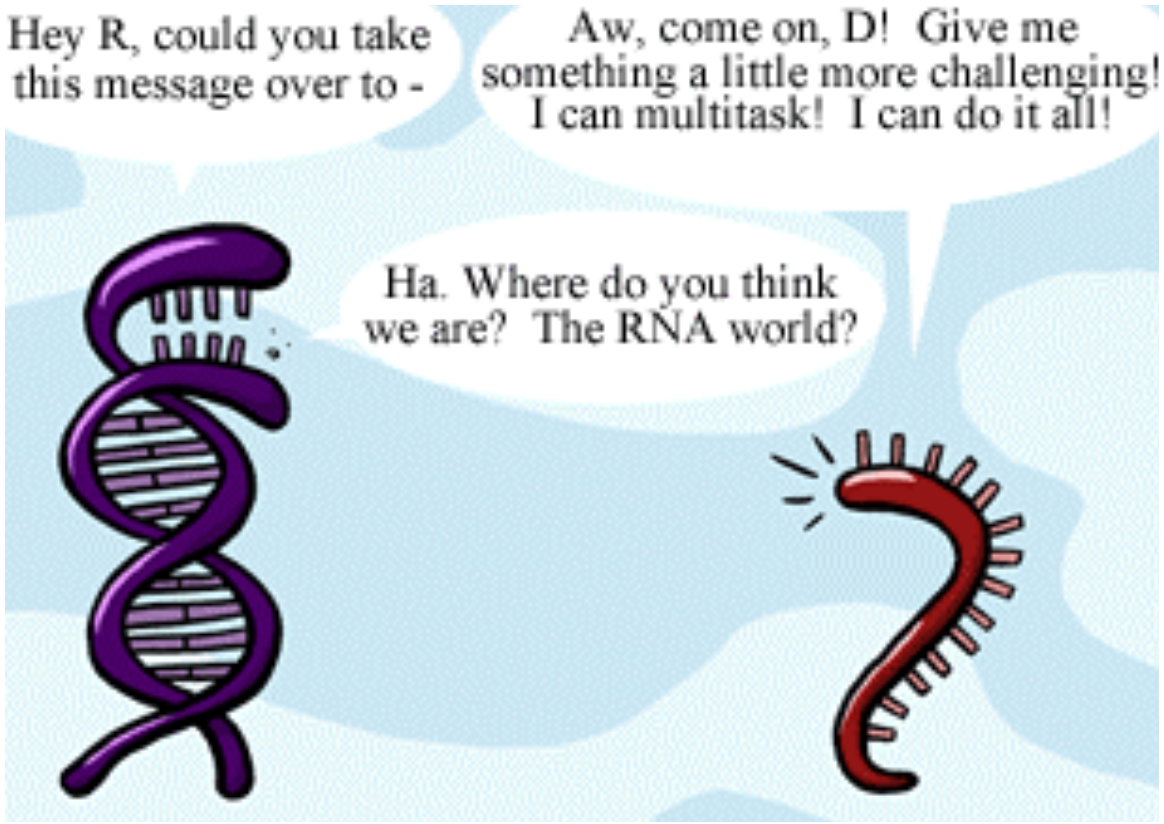
microRNA-based therapy

The perfect storm of tiny RNAs

NATURE MEDICINE VOLUME 14 | NUMBER 10 | OCTOBER 2008






Hey R, could you take this message over to -
Aw, come on, D! Give me something a little more challenging! I can multitask! I can do it all!
Ha. Where do you think we are? The RNA world?

Nobel price Medicine 2006:

Andrew Z. Fire
Craig Mello

Nobelprize.org
The Official Web Site of the Nobel Prize

Evolution of RNAi

1990

1990 Post transcriptional gene silencing (PTGS)

1992

1992 Quelling in Neurospora

1998

1998-2001 RNAi in yeast, Drosophila, plants, trypanosomes

1998 "RNAi" in C. elegans

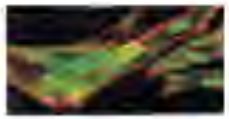
C. elegans +/- RNA

2001

2001 Successful siRNA experiments in mammalian cells

2002

2002 Science named RNAi "Technology of the Year"



2002 Recombinant Dicer generated siRNA

2003

- Improved synthetic design
- Modified reagents
- RNAi mechanism
- Toxicity responses
- Controls

2004

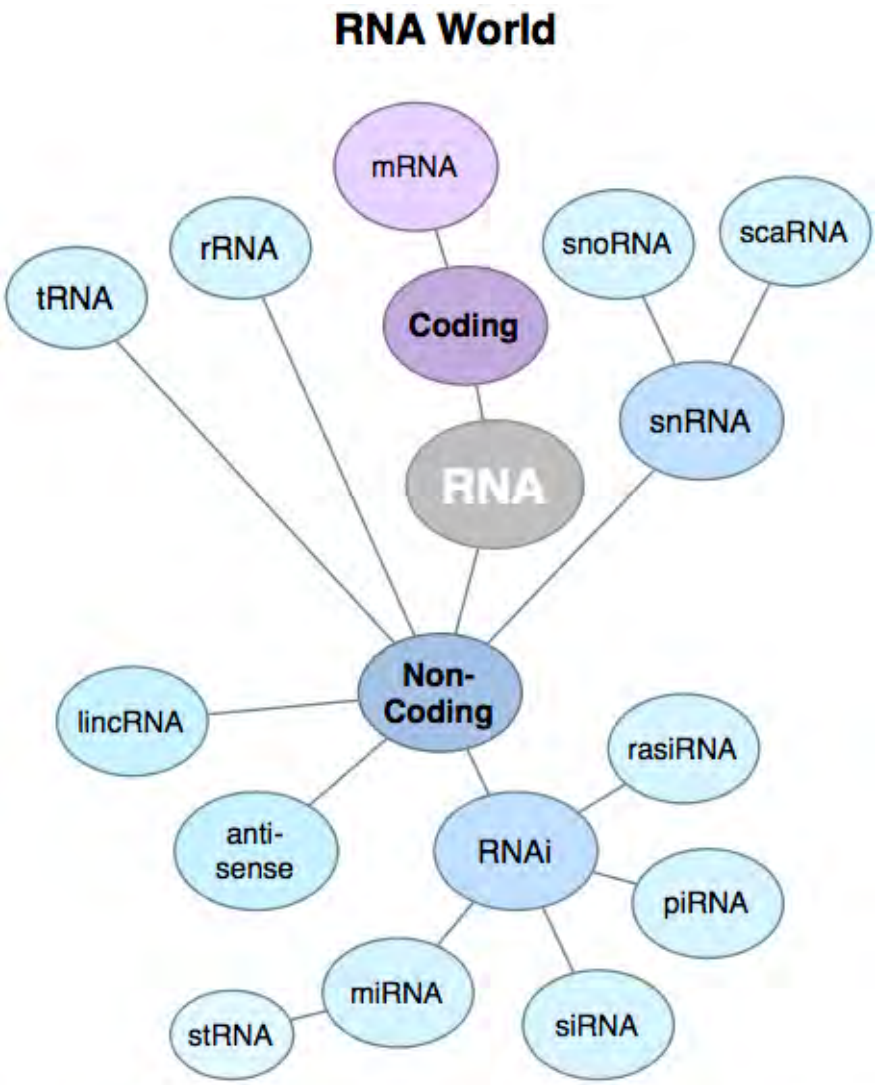
2005

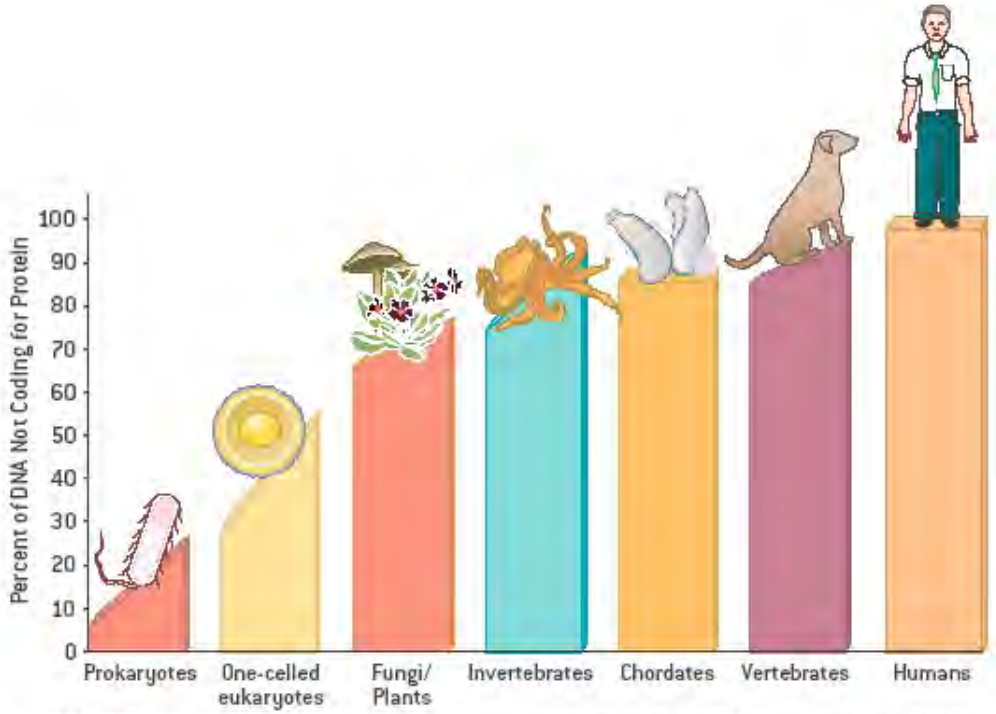
- Specificity concerns
- Super-active reagents
- More on *in vivo*
- Unique apps

2006

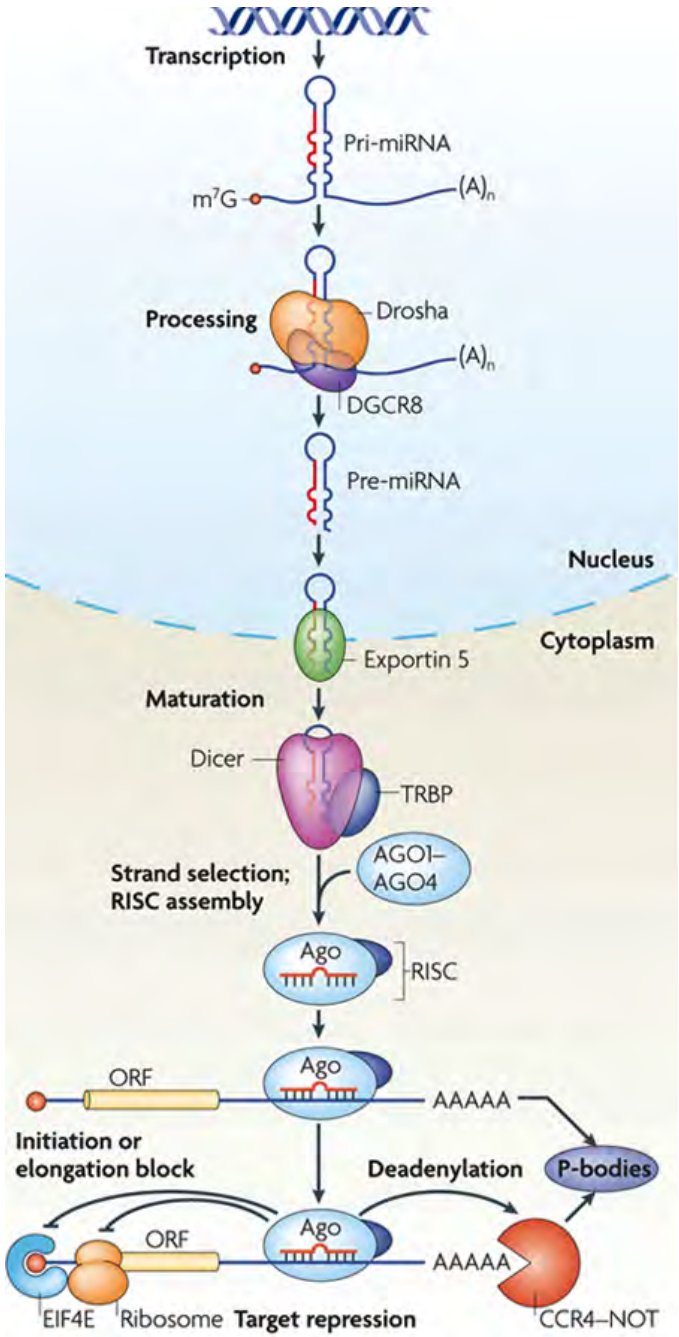
Nobel Prize Fire & Mello

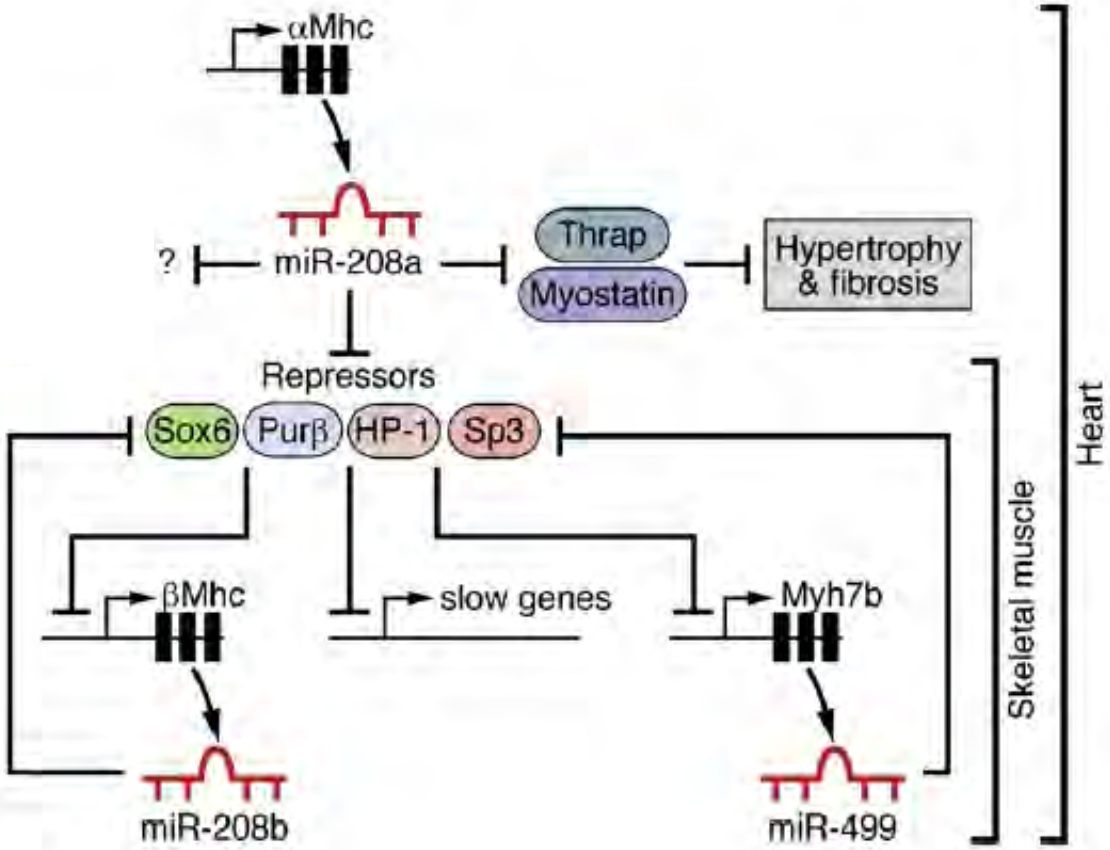
- Design improvements
- Validated reagents
- *In vivo* applications
- Micro RNA
- Large screens


RNA World
mRNA
rRNA
tRNA
Coding
snoRNA
scaRNA
snRNA
RNA
Non-
Coding
lincRNA
anti-
sense
RNAi
rasiRNA
piRNA
miRNA
stRNA
siRNA



NONPROTEIN-CODING SEQUENCES make up only a small fraction of the DNA of prokaryotes. Among eukaryotes, as their complexity increases, generally so, too, does the proportion of their DNA that does not code for protein. The noncoding sequences have been considered junk, but perhaps it actually helps to explain organisms' complexity.


Transcription
Pri-miRNA
m7G
(A)n
Processing
Drosha
(A)n
DGCR8
Pre-miRNA
Nucleus
Cytoplasm
Exportin 5
Maturation
Dicer
TRBP
Strand selection;
RISC assembly
AGO1–
AGO4
Ago
RISC
ORF
Ago
AAAAA
Initiation or
elongation block
Deadenylation
P-bodies
ORF
Ago
AAAAA
EIF4E
Ribosome
Target repression
CCR4–NOT


αMhc
?
miR-208a
Thrap
Myostatin
Hypertrophy & fibrosis
Repressors
Sox6
Purβ
HP-1
Sp3
βMhc
slow genes
Myh7b
miR-208b
miR-499
Skeletal muscle
Heart

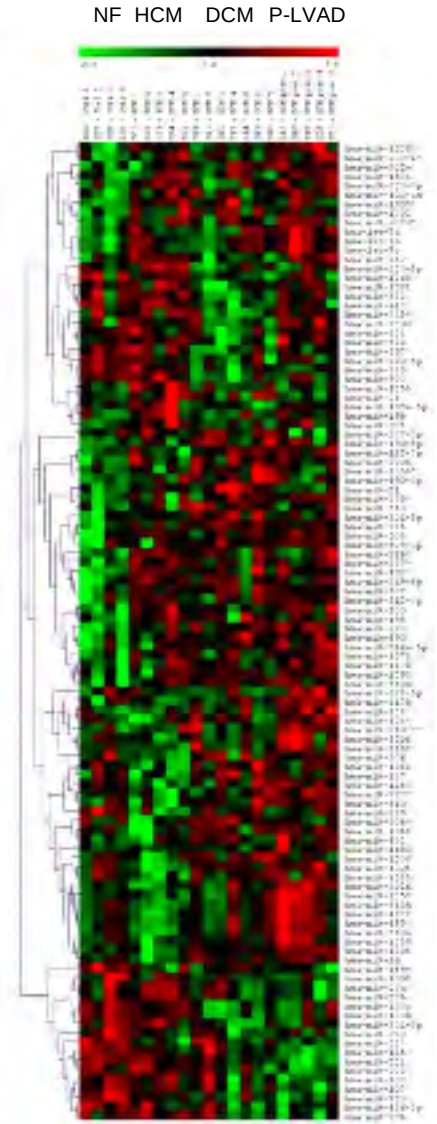
the world of noncoding RNA

microRNA expression

microRNA regulation

microRNA function

microRNA-based therapy


NF HCM DCM P-LVAD

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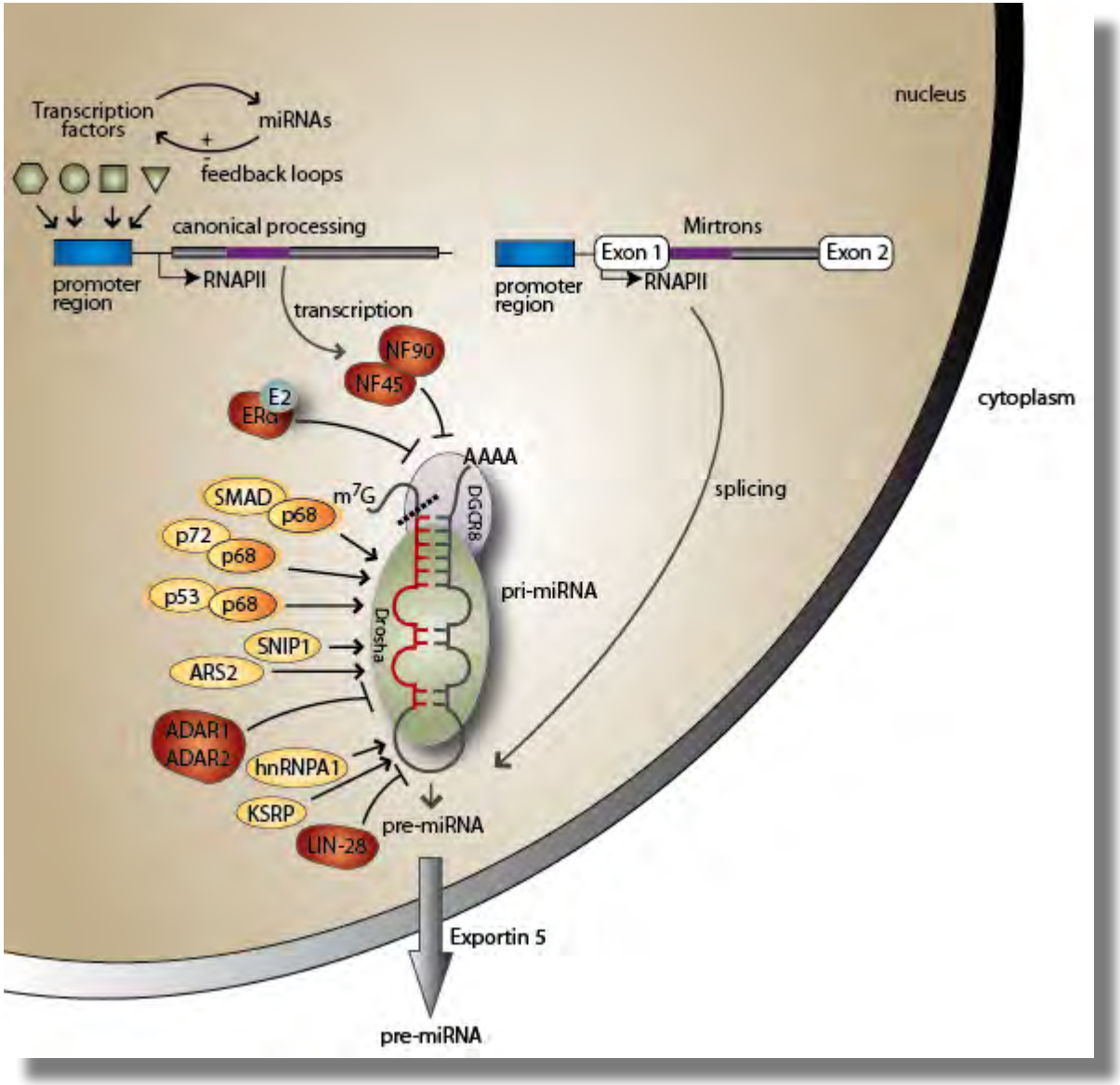
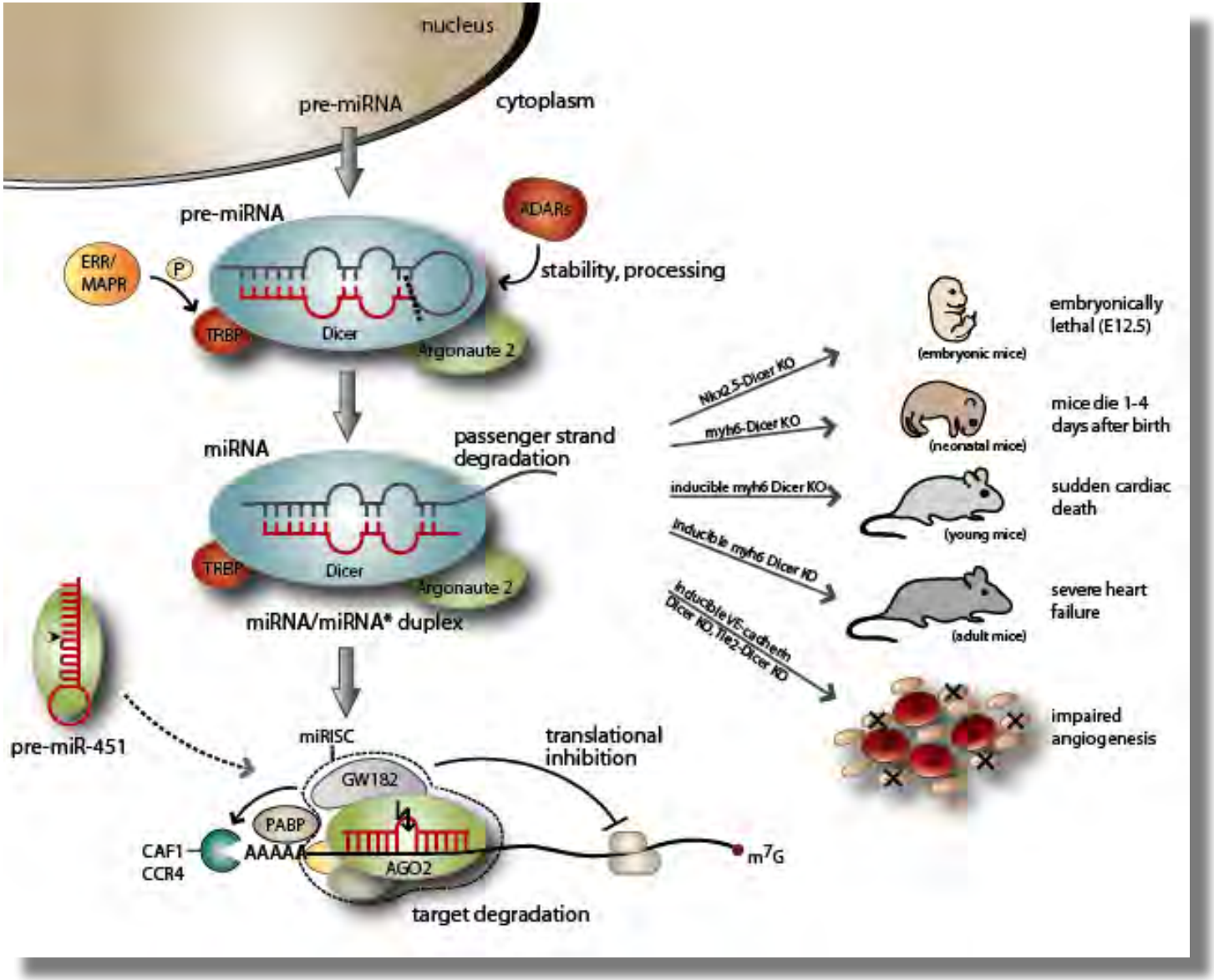
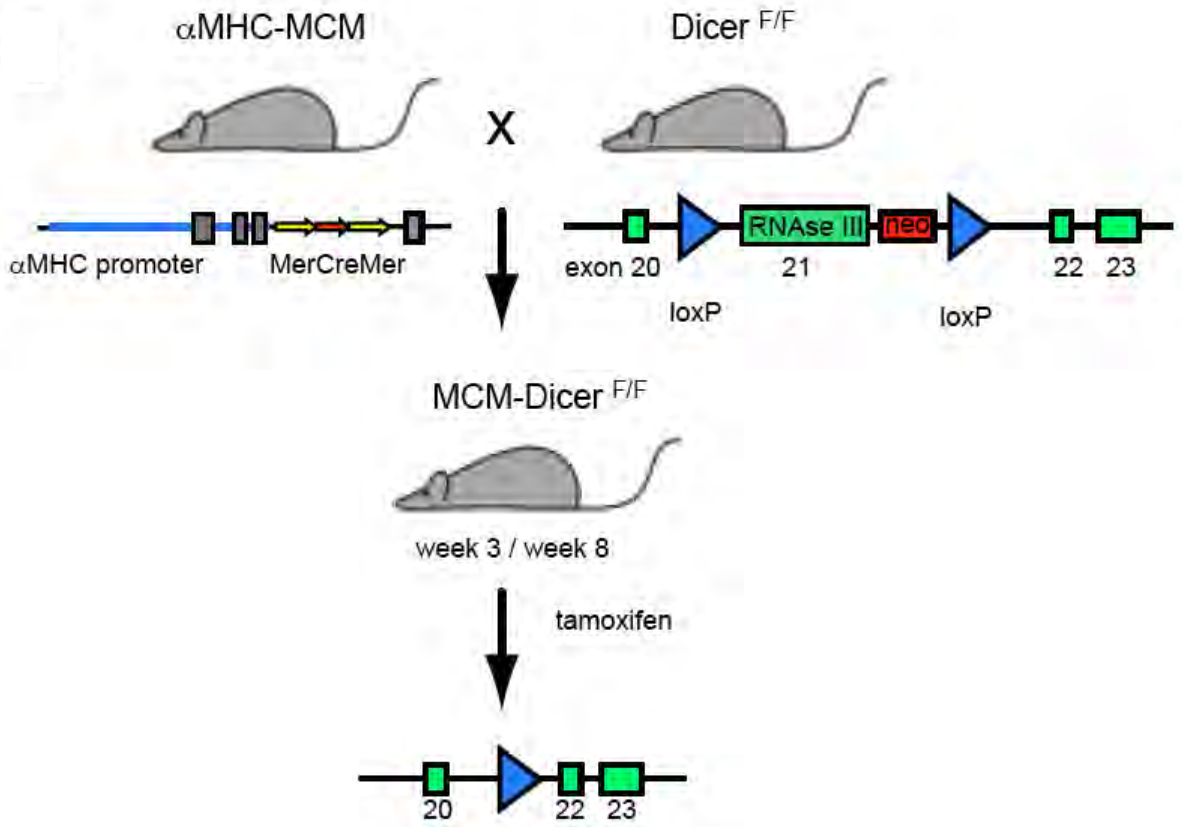


Bauersachs & Thum,
Circ Res (in press)

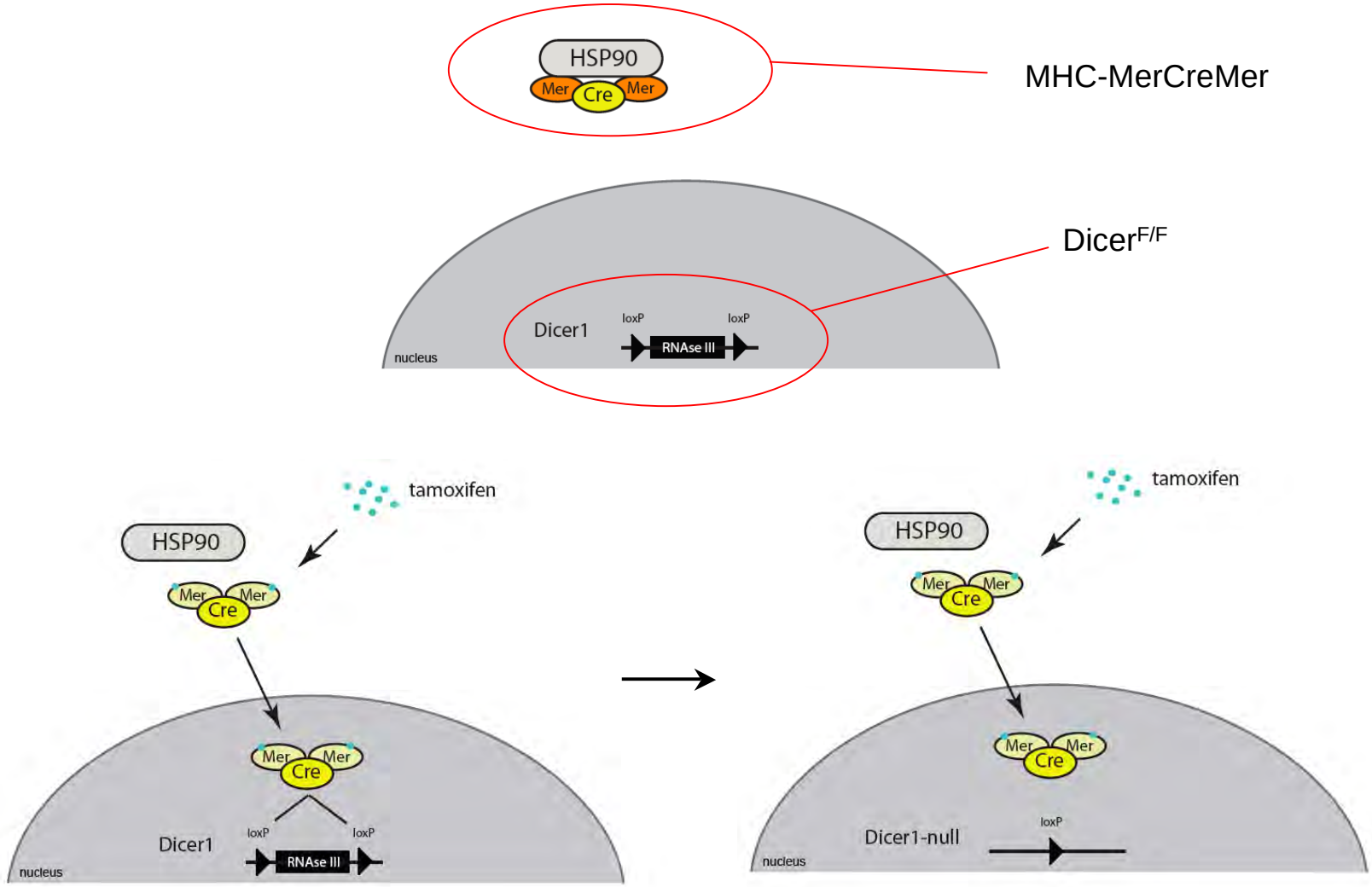


Bauersachs & Thum,
Circ Res (in press)



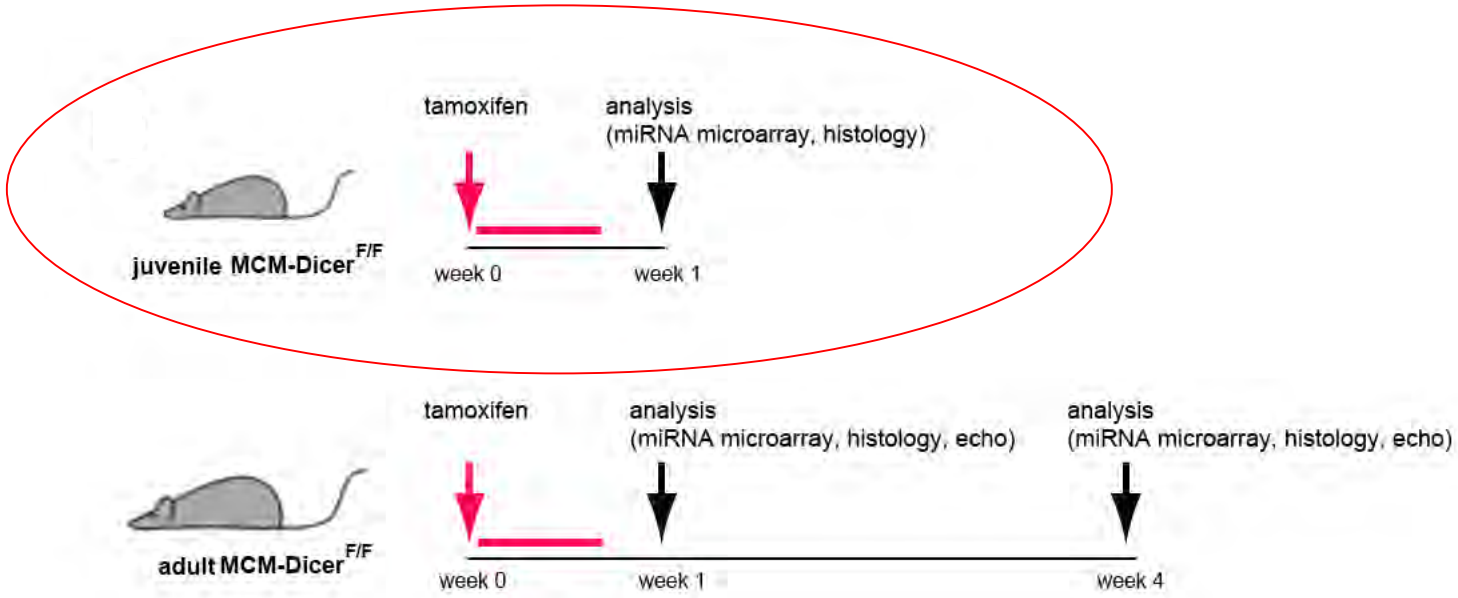
Da Costa Martins *et al*. *Circulation.* 2008;118:1567

Conditional, heart-restricted knockout approach



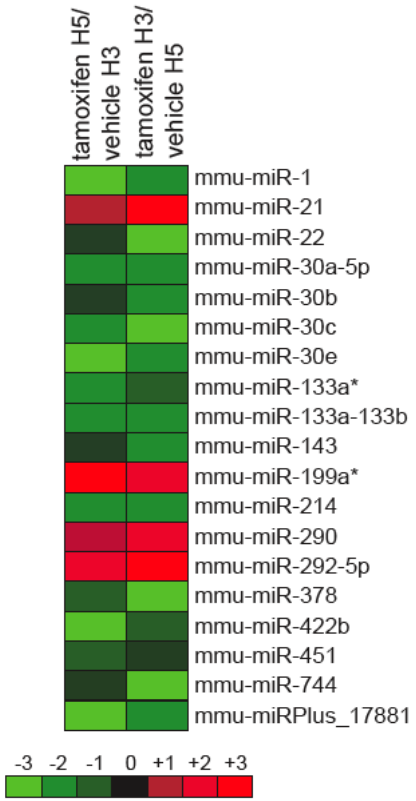
Da Costa Martins *et al*. *Circulation.* 2008;118:1567

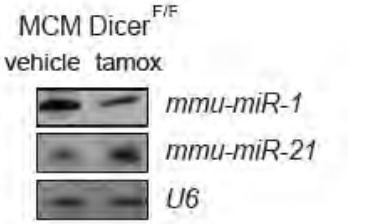
Experimental set up Dicer study

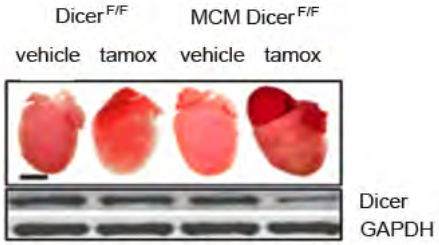


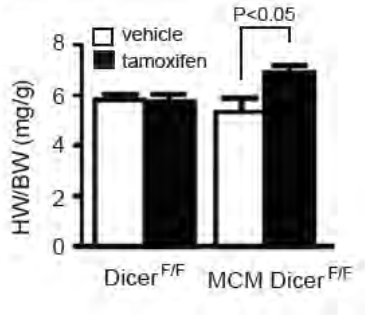
Da Costa Martins *et al*. *Circulation.* 2008;118:1567

Dicer depletion in juvenile mice



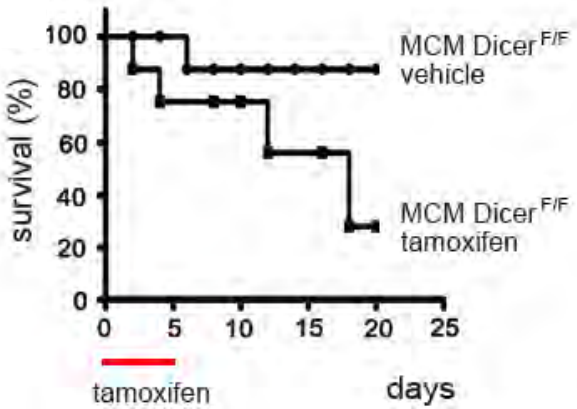


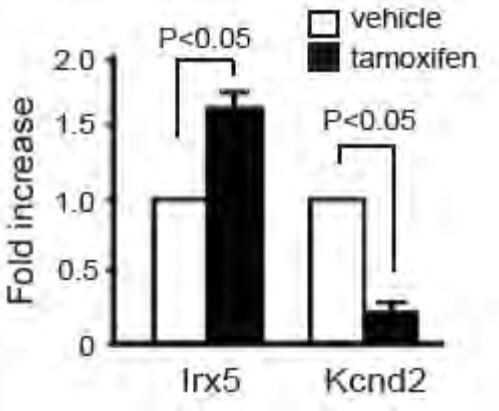




Da Costa Martins *et al*. *Circulation.* 2008;118:1567

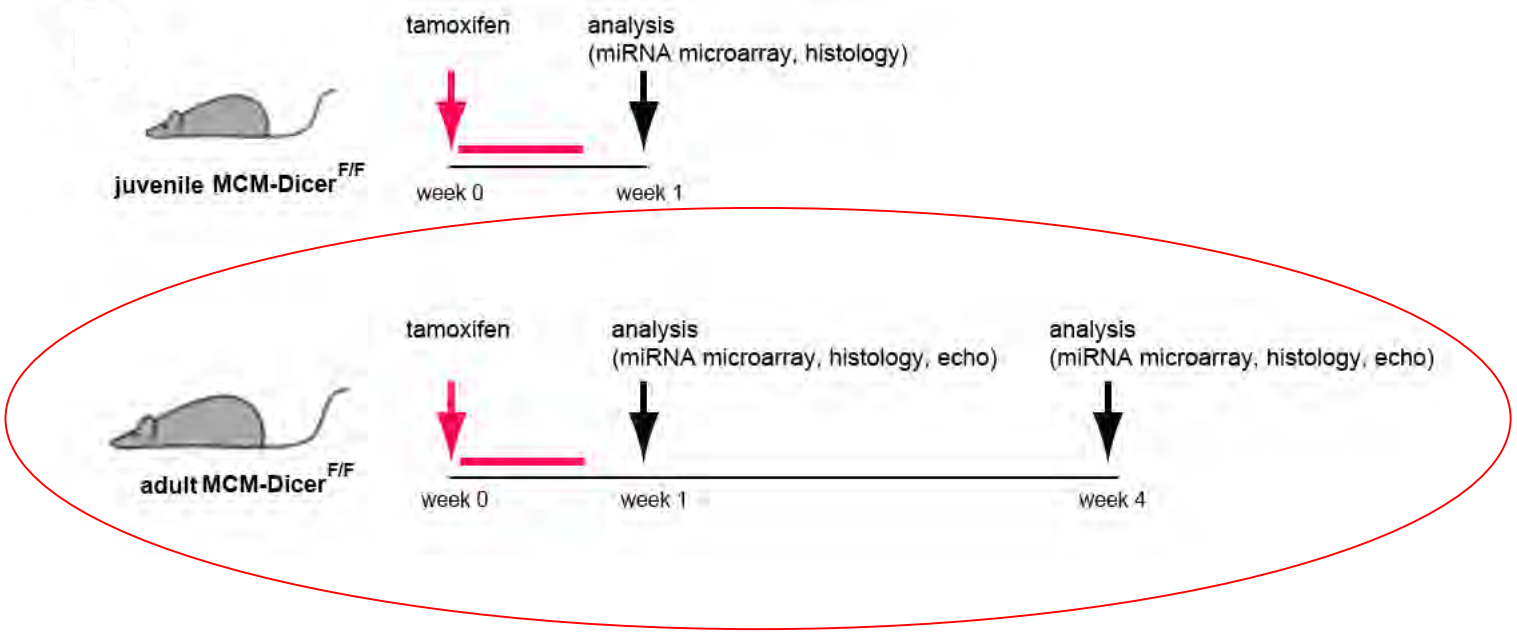
Dicer depletion in juvenile mice causes sudden death





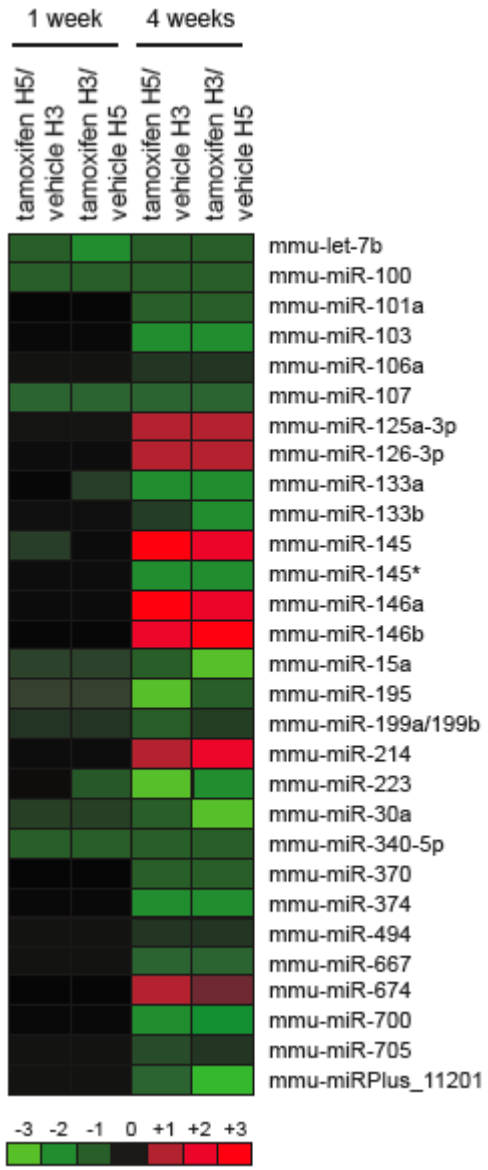
Da Costa Martins *et al*. *Circulation.* 2008;118:1567

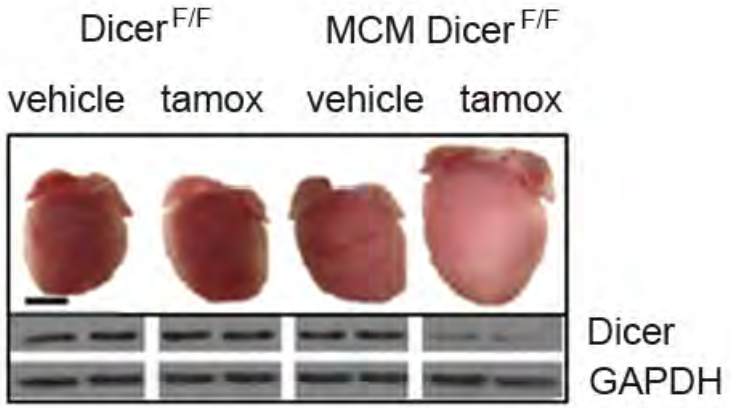
Experimental set up Dicer study

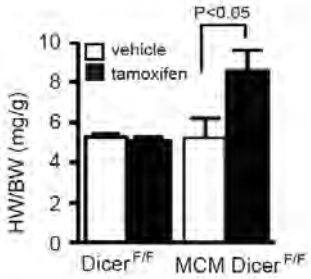


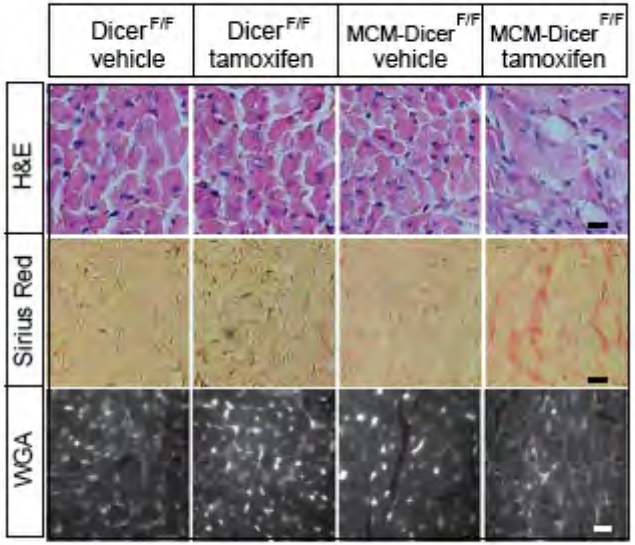
Da Costa Martins *et al*. *Circulation.* 2008;118:1567

Adult-onset Dicer depletion provokes spontaneous remodeling



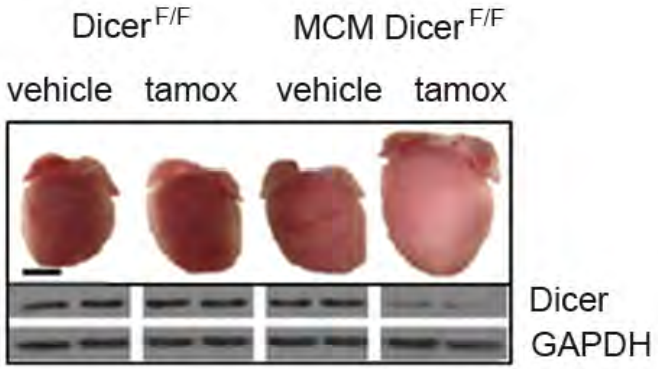


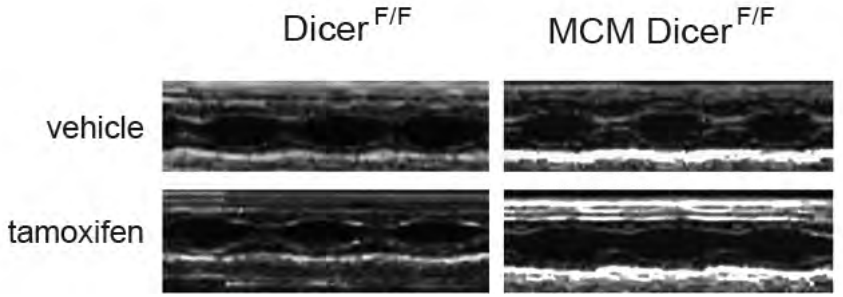


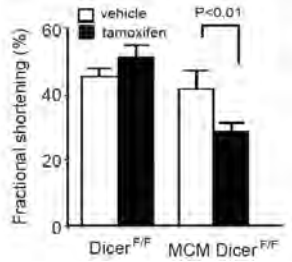


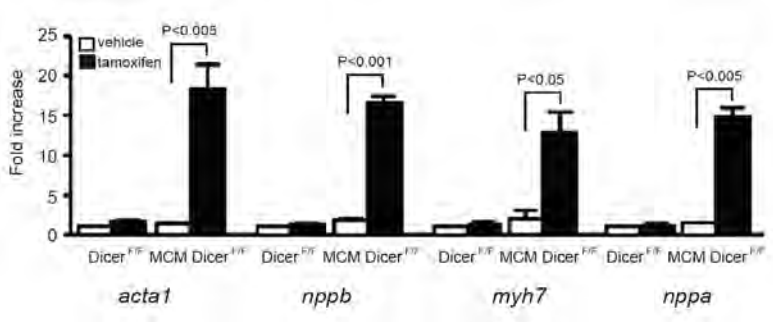
Da Costa Martins *et al*. *Circulation.* 2008;118:1567

Adult-onset Dicer depletion provokes cardiac dysfunction









Da Costa Martins *et al*. *Circulation.* 2008;118:1567

the world of noncoding RNA

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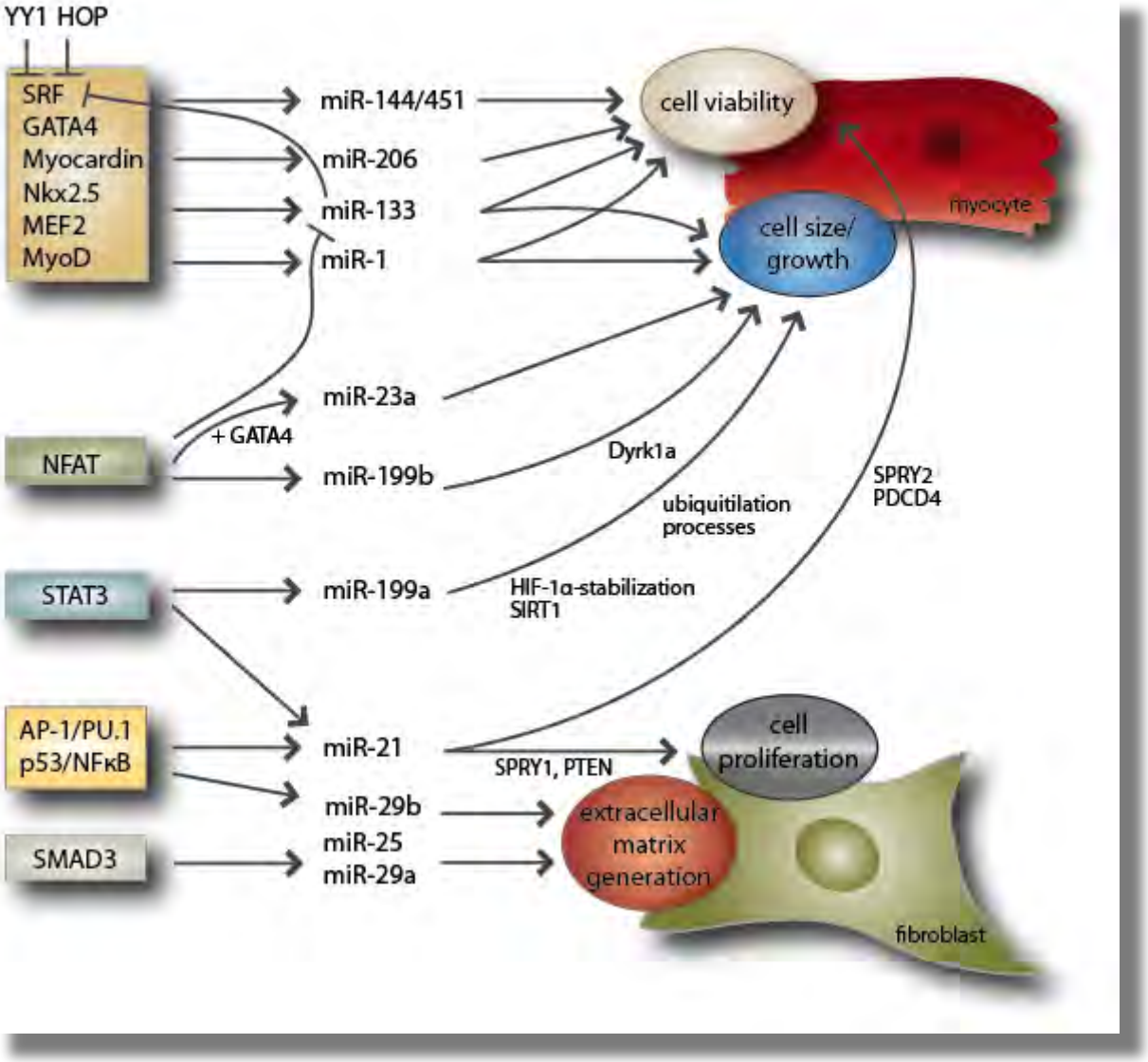
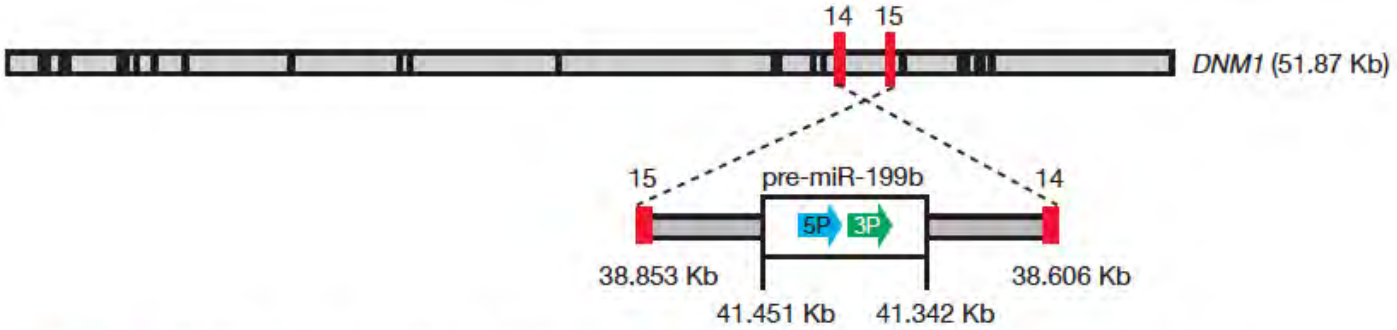
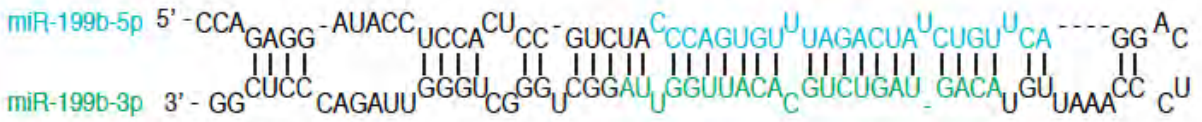
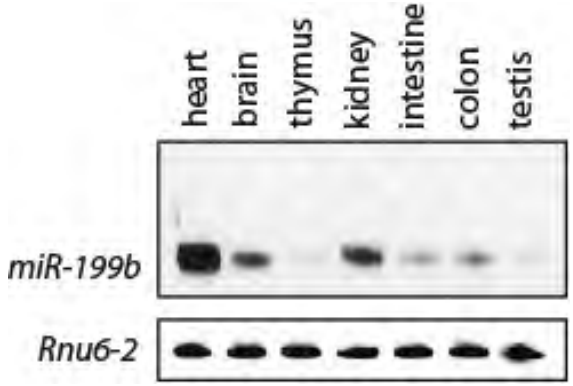


Bauersachs &
Thum,
Circ Res (in press)

microRNA-199b



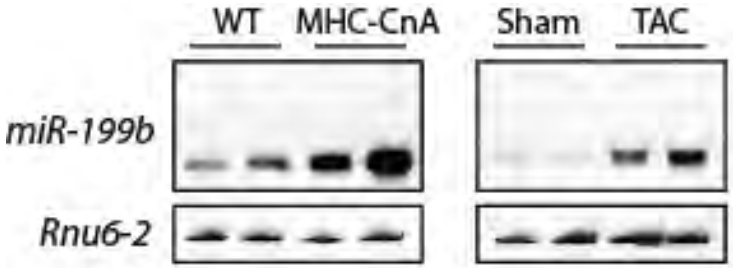


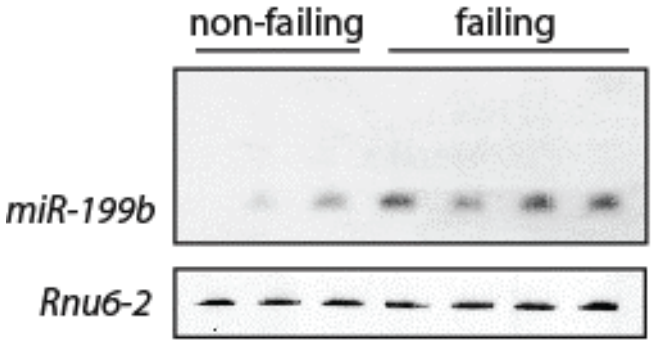


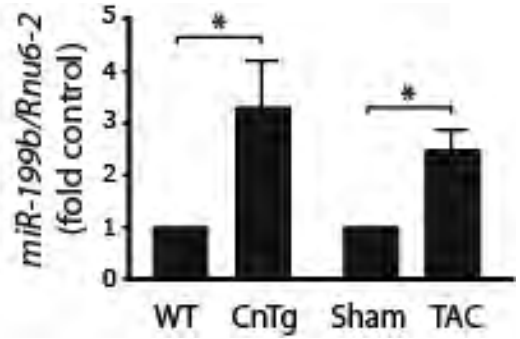
	5' 3'
Human	CCCAGUGUUUAGACUAUCUGUUC
Orangutan	GUGUUUAGACUAUCUGUUC
Horse	CCCAGUGUUUAGACUAUCUGUUC
Cow	CCCAGUGUUUAGACUAUCUGUUC
Pig	CCCAGUGUUUAGACUAUCUGUU
Mouse	CCCAGUGUUUAGACUACCUGUUC
Frog	CCCAGUGUUCAGACUACGUGUUC

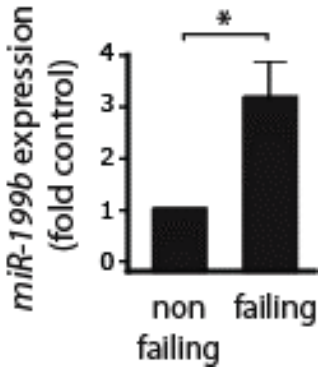
Da Costa Martins, Salic *et al*. *Nature Cell Biol.* 2010;12:1220

miR-199b is upregulated in rodent and human heart failure



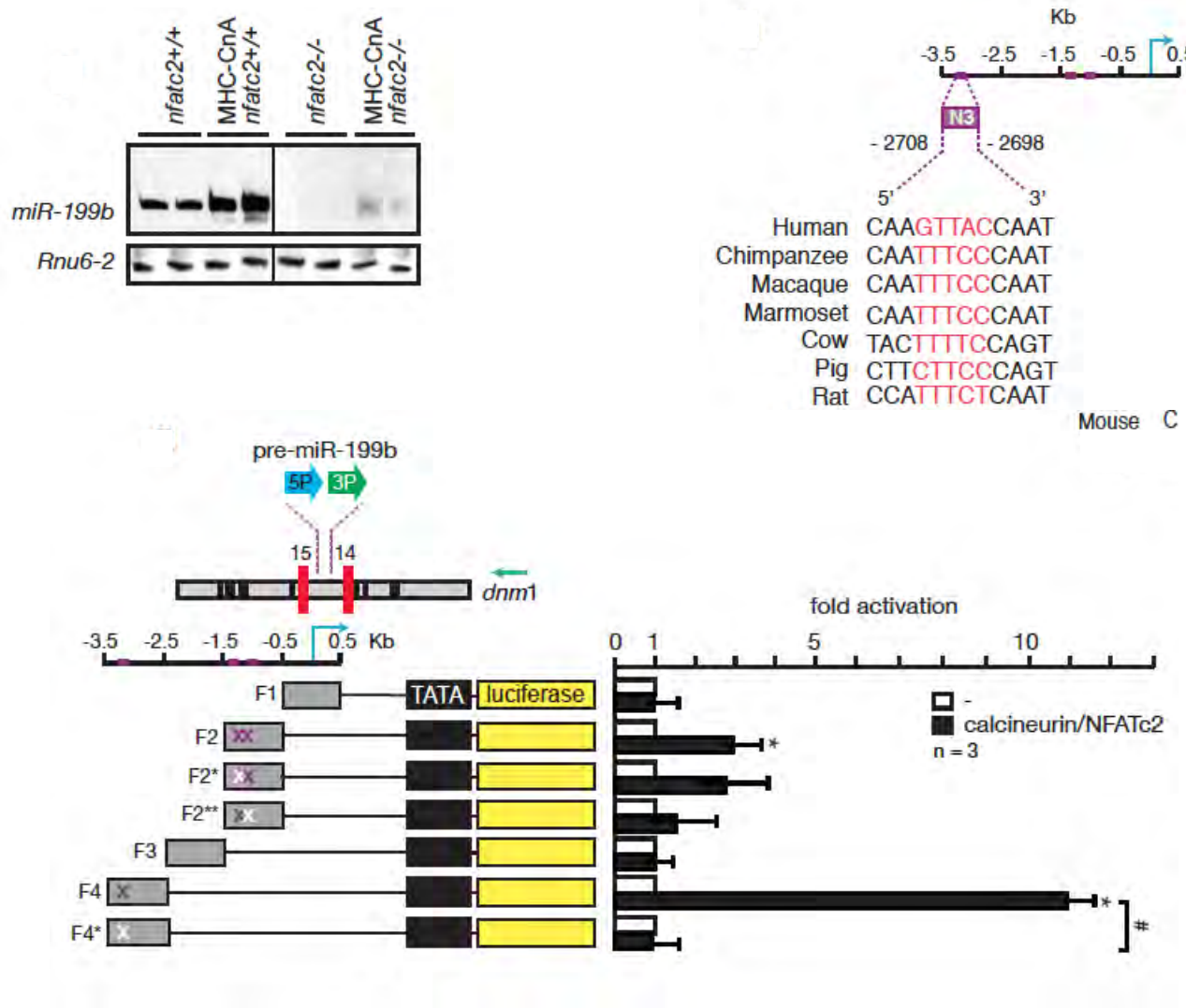






Da Costa Martins, Salic *et al*. *Nature Cell Biol.* 2010;12:1220

miR-199b is a direct NFAT target gene



Da Costa Martins, Salic *et al*. *Nature Cell Biol.* 2010;12:1220

Dyrk1a: **D**ual-specificity t**y**rosine-(Y)-phosphorylation **r**egulated **k**inase **1a**

A genome-wide *Drosophila* RNAi screen identifies DYRK-family kinases as regulators of NFAT

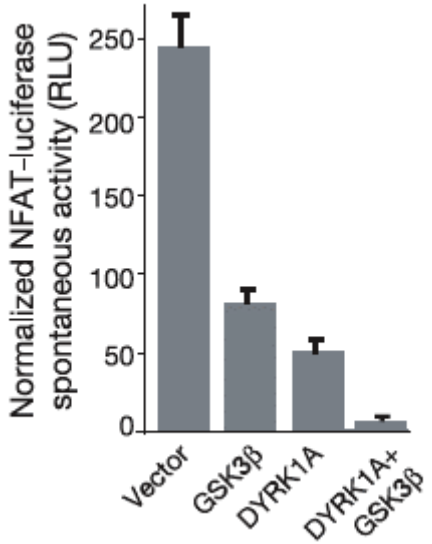
Yousang Gwack[1,2*], Sonia Sharma[1,2*], Julie Nardone[1†], Bogdan Tanasa[1], Alina Iuga[1,2], Sonal Srikanth[1,2], Heidi Okamura[1,2†], Diana Bolton[1†], Stefan Feske[1,3], Patrick G. Hogan[1] & Anjana Rao[1,2]

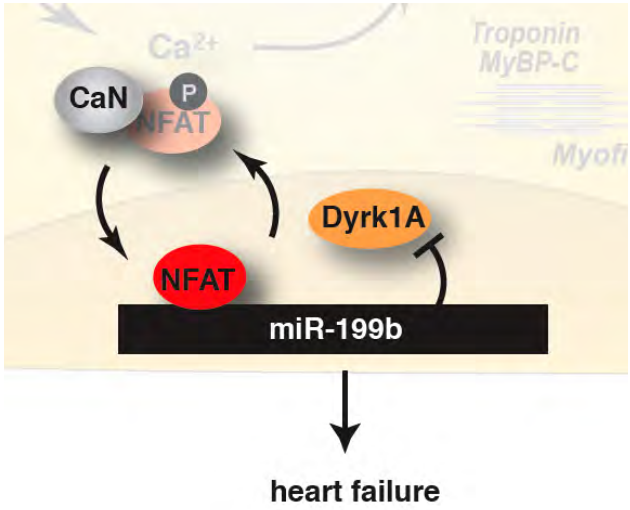
Vol 441|1 June 2006|**doi:10.1038/nature04631**

NFAT dysregulation by increased dosage of *DSCR1* and *DYRK1A* on chromosome 21

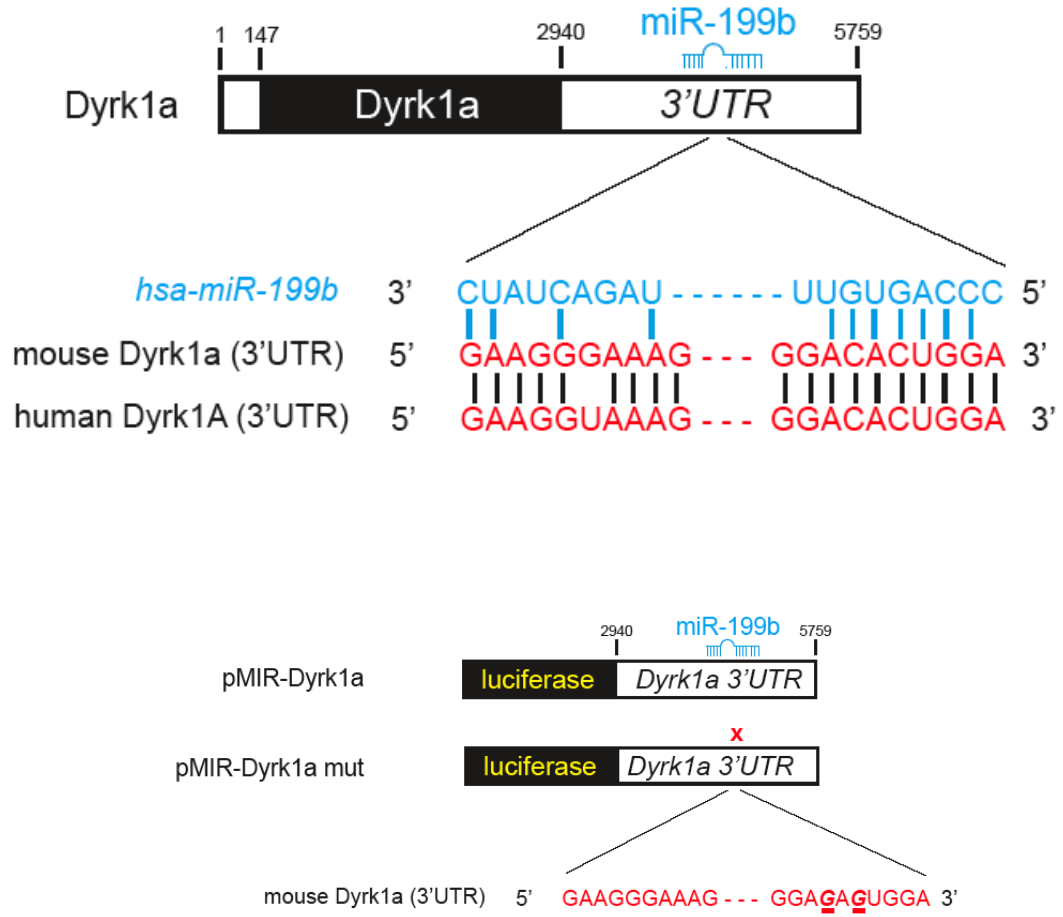
Joseph R. Arron[1*], Monte M. Winslow[2*], Alberto Polleri[1*], Ching-Pin Chang[3], Hai Wu[1], Xin Gao[1], Joel R. Neilson[2], Lei Chen[1], Jeremy J. Heit[4], Seung K. Kim[4], Nobuyuki Yamasaki[7], Tsuyoshi Miyakawa[7], Uta Francke[5], Isabella A. Graef[1*] & Gerald R. Crabtree[1,4,6]

doi:10.1038/nature04678



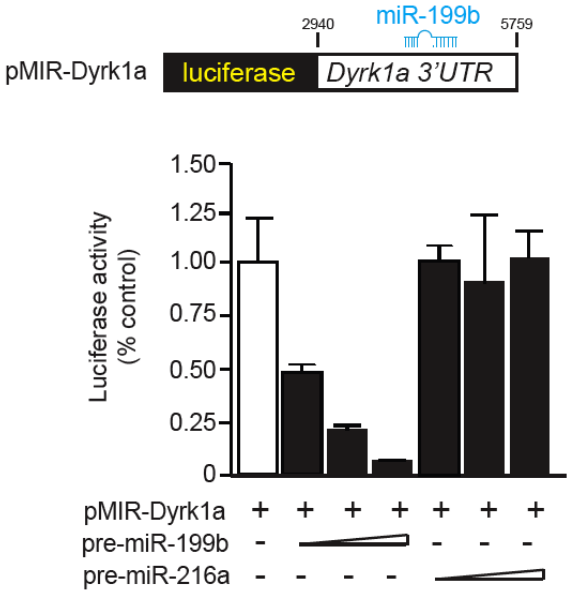


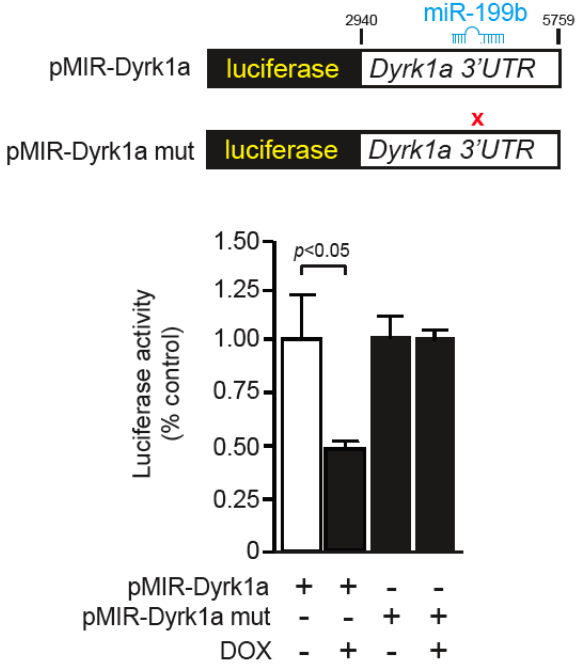
A conserved seed region in the 3’UTR of Dyrk1a



Da Costa Martins, Salic *et al*. *Nature Cell Biol.* 2010;12:1220

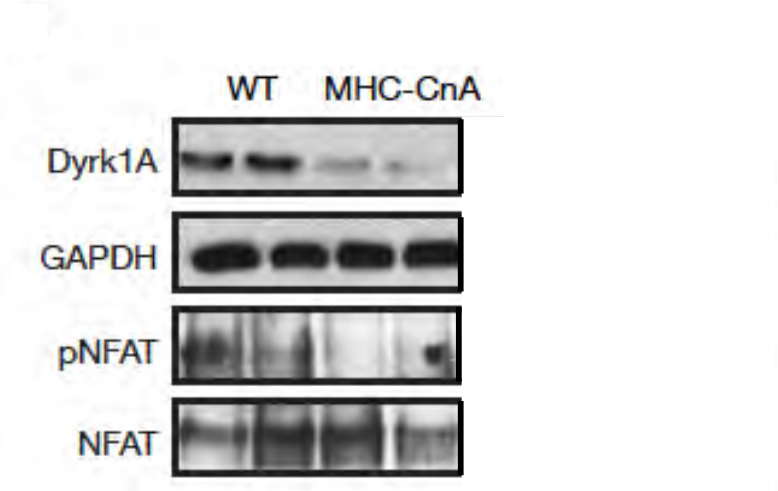
Dyrk1a is a direct target of miR-199b





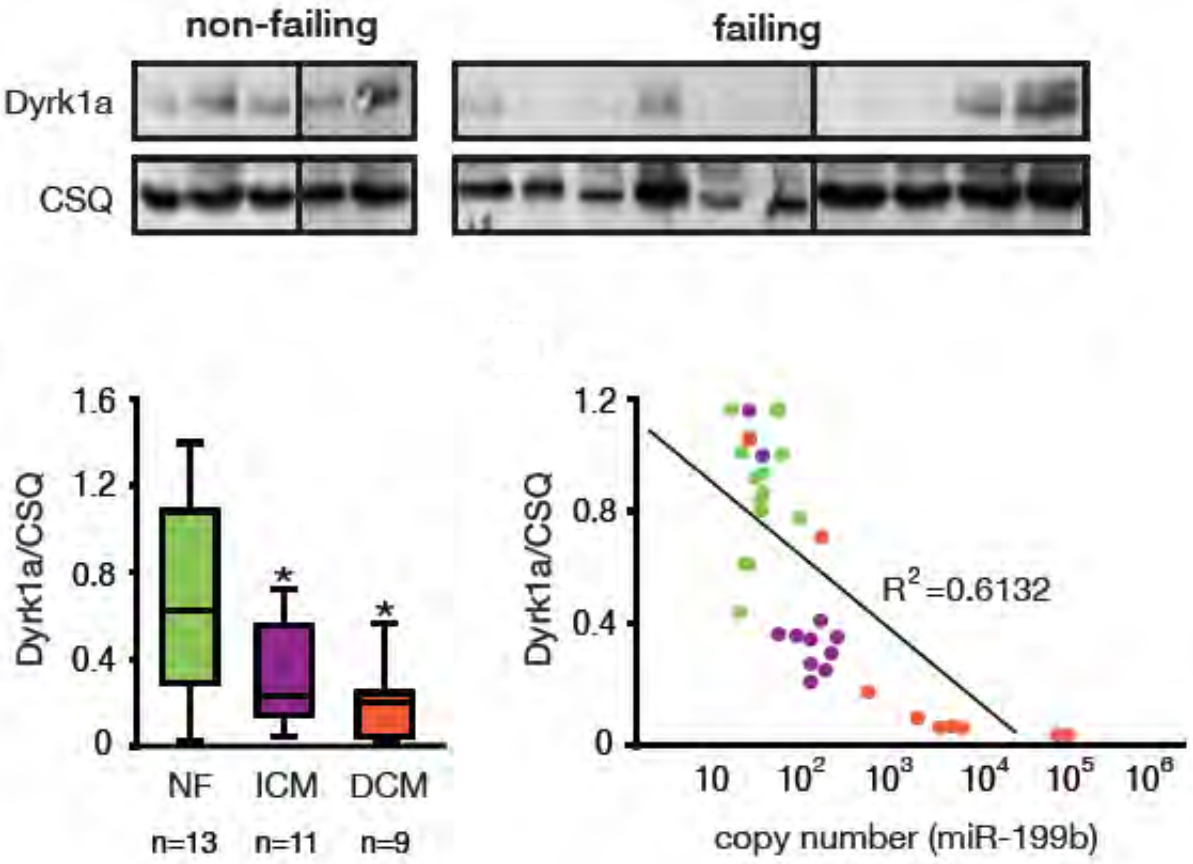
Da Costa Martins, Salic *et al*. *Nature Cell Biol.* 2010;12:1220

Dyrk1a and miR-199b expression inversely correlate in the failing mouse heart



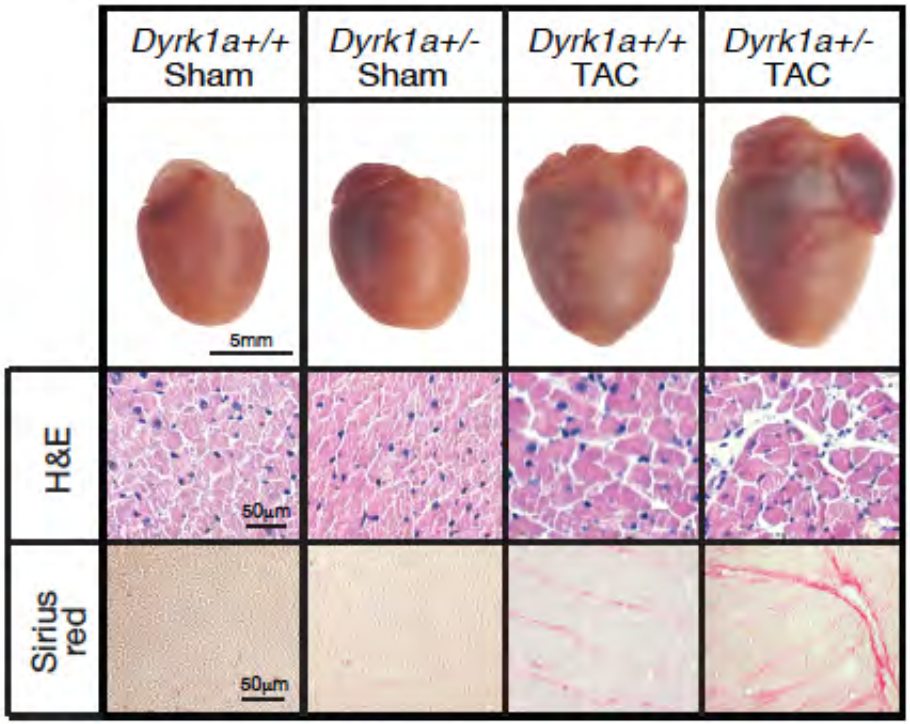
Da Costa Martins, Salic *et al*. *Nature Cell Biol.* 2010;12:1220

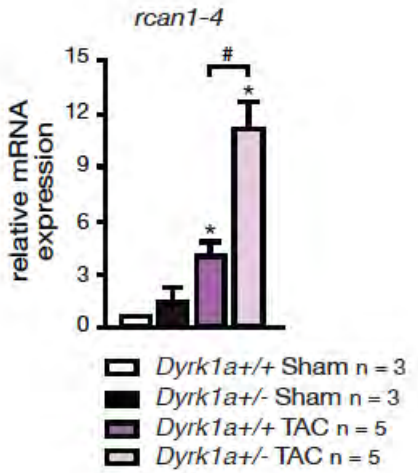
Dyrk1a and miR-199b inversely correlate in human failing hearts



Da Costa Martins, Salic *et al*. *Nature Cell Biol.* 2010;12:1220

Dyrk1a haploinsufficient mice are sensitized to stress stimuli





Da Costa Martins, Salic *et al*. *Nature Cell Biol.* 2010;12:1220

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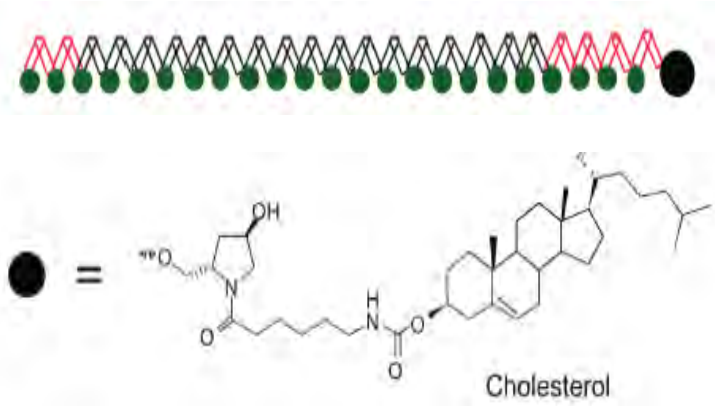
microRNA function

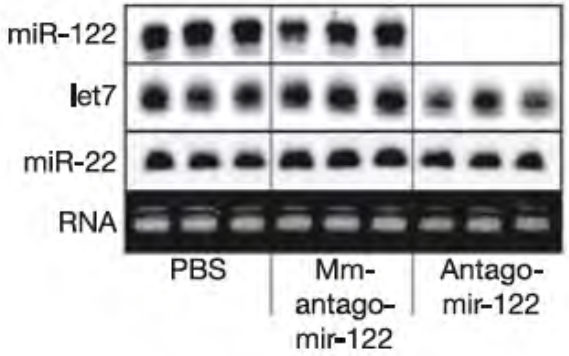
microRNA-based therapy

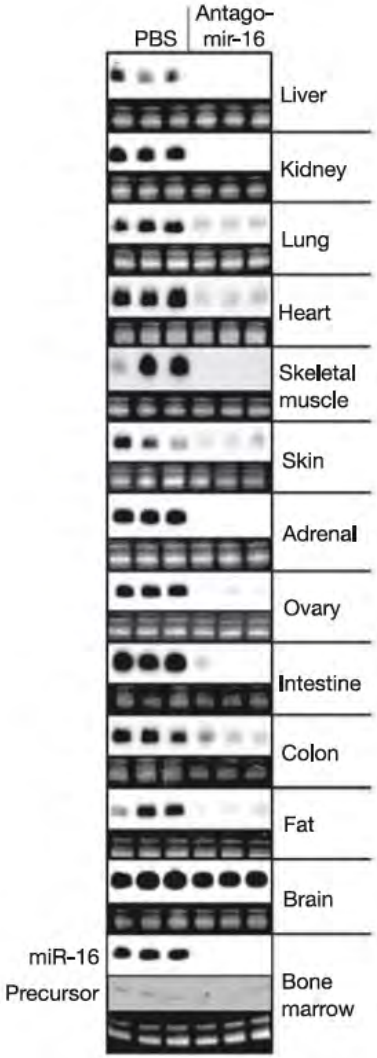
Silencing of microRNAs *in vivo* with 'antagomirs'

Jan Krützfeldt[1], Nikolaus Rajewsky[3], Ravi Braich[4], Kallanthottathil G. Rajeev[4], Thomas Tuschl[2], Muthiah Manoharan[4] & Markus Stoffel[1]

Vol 438|1 December 2005|**doi:10.1038/nature04303**







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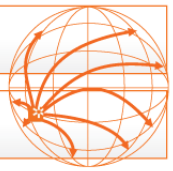
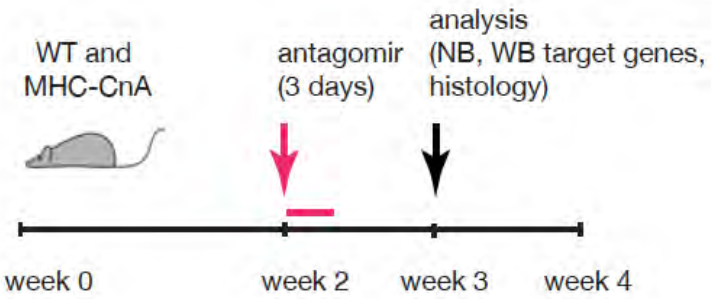
REGULUS THERAPEUTICS™

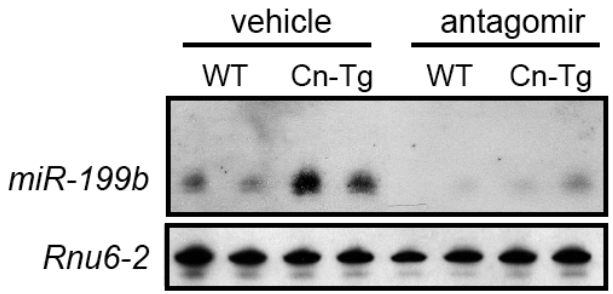
Technology Applies to Multiple Areas Using Therapeutics that either Antagonize (anti-miRs) or Agonize (mimics) microRNAs

FIBROSIS	Demonstrated therapeutic activity in multiple animal models of fibrosis	sanofi aventis
HCV	Developing HCV therapy; Regulus controls key IP	gsk
IMMUNO-INFLAMMATORY	Multiple targets for immune-related diseases	gsk
METABOLISM & CV	Multiple targets for metabolic & cardiovascular diseases	
ONCOLOGY	Novel therapeutic approach for HCC	
EXPLORATORY	Multiple and diverse global collaborations with leading academic institutions: over 30	



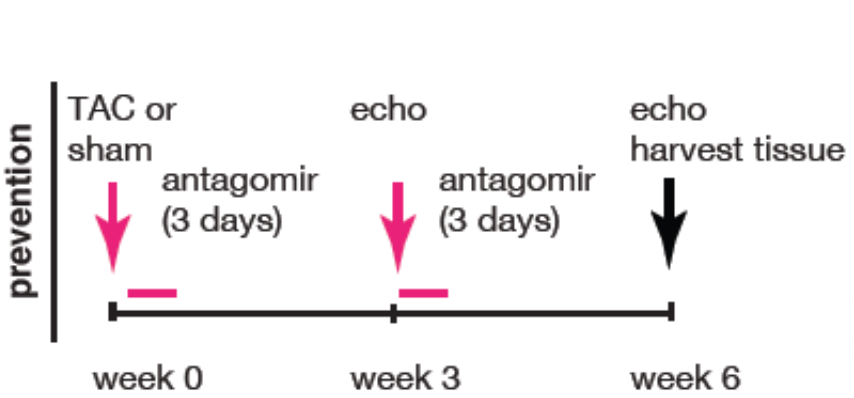
antagomir-199b rescues calcineurin-driven cardiac remodeling

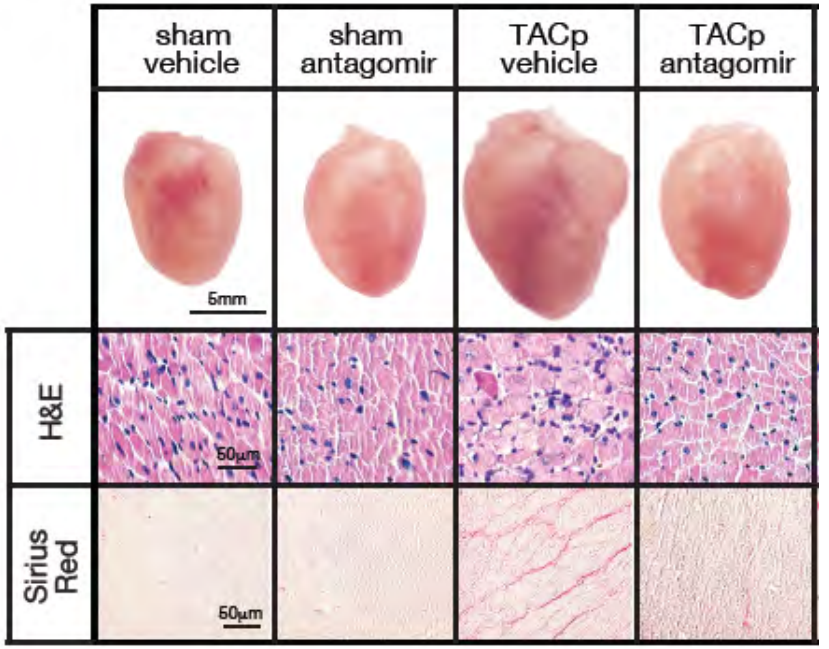


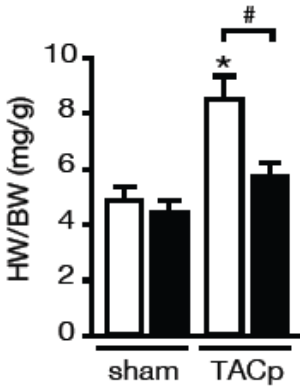


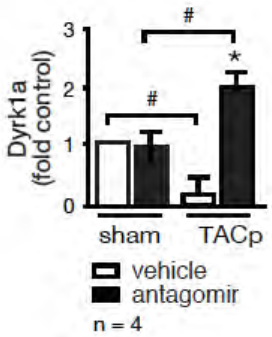
Da Costa Martins, Salic *et al*. *Nature Cell Biol.* 2010;12:1220

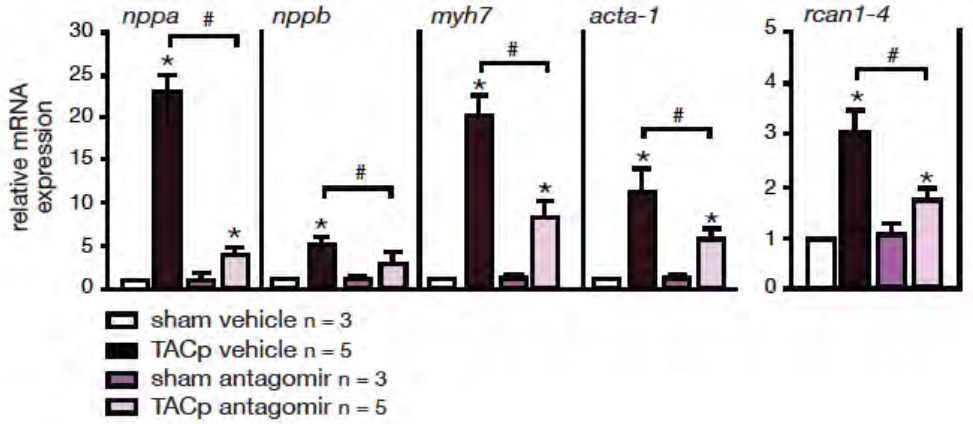
Antagomir-199b prevents pressure overload-induced cardiac hypertrophy





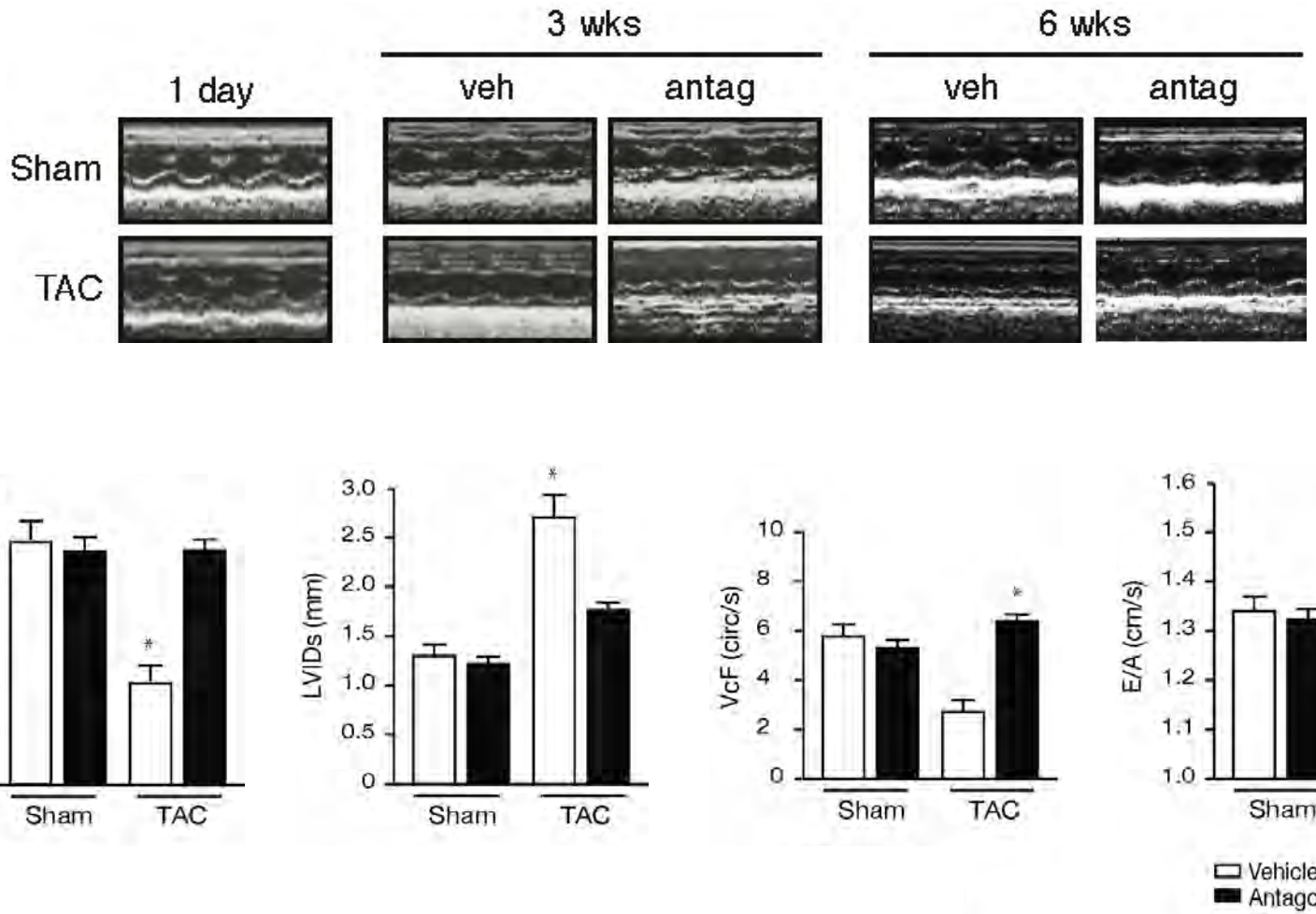




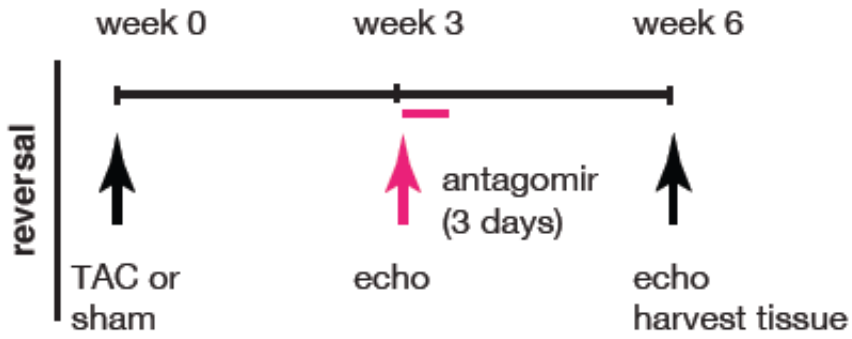


Da Costa Martins, Salic *et al*. *Nature Cell Biol.* 2010;12:1220

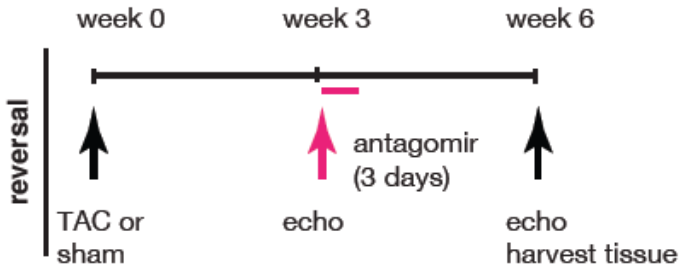
Antagomir-199b restores cardiac geometry and contractility

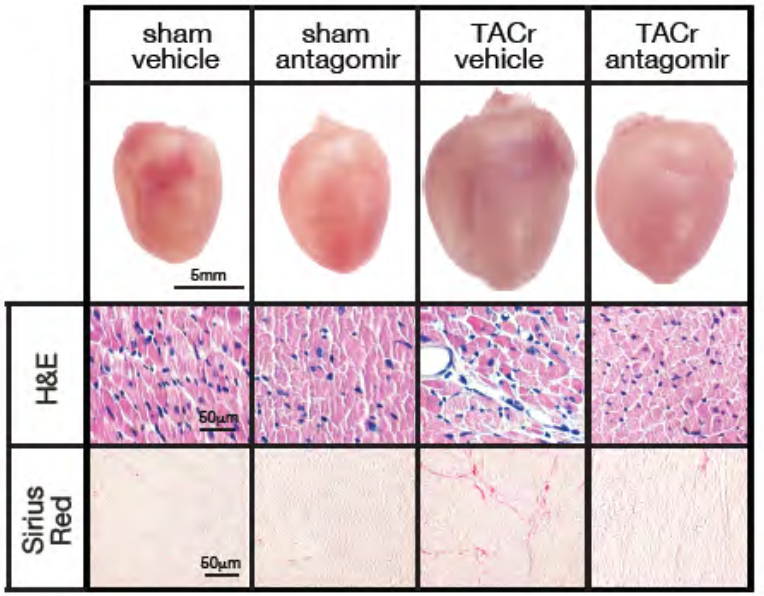


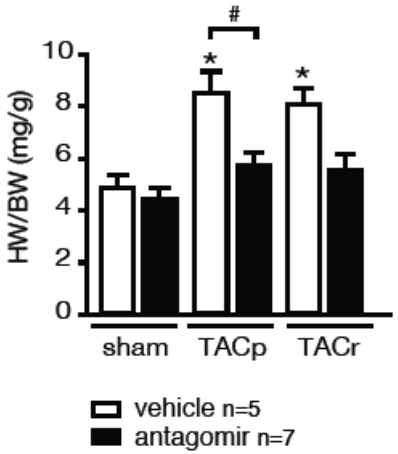
Da Costa Martins, Salic *et al*. *Nature Cell Biol.* 2010;12:1220

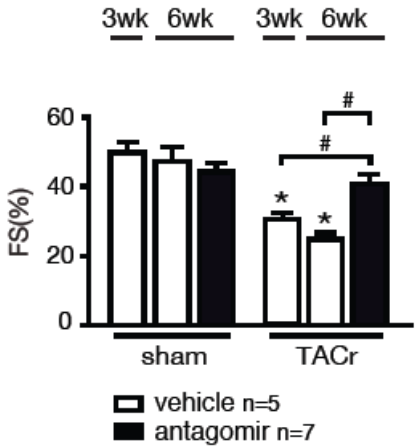

week 0
week 3
week 6
reversal
antagomir
(3 days)
TAC or
sham
echo
echo
harvest tissue

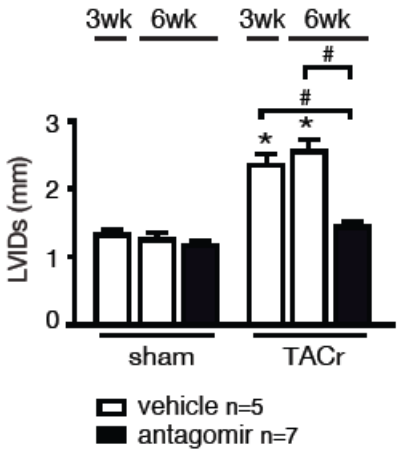
Antagomir-199b reverses cardiac remodeling, dysfunction and dilation











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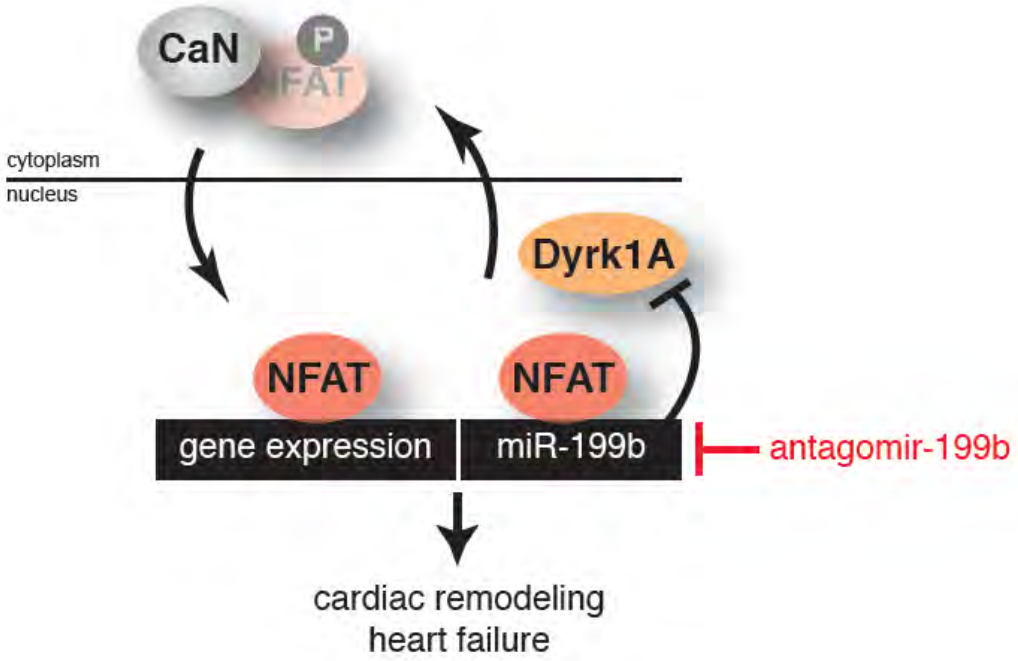
CaN
P
NFAT
cytoplasm
nucleus
Dyrk1A
NFAT
NFAT
gene expression
miR-199b
antagomir-199b
cardiac remodeling
heart failure

the world of noncoding RNA

microRNA expression

microRNA regulation

microRNA function

microRNA-based therapy

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