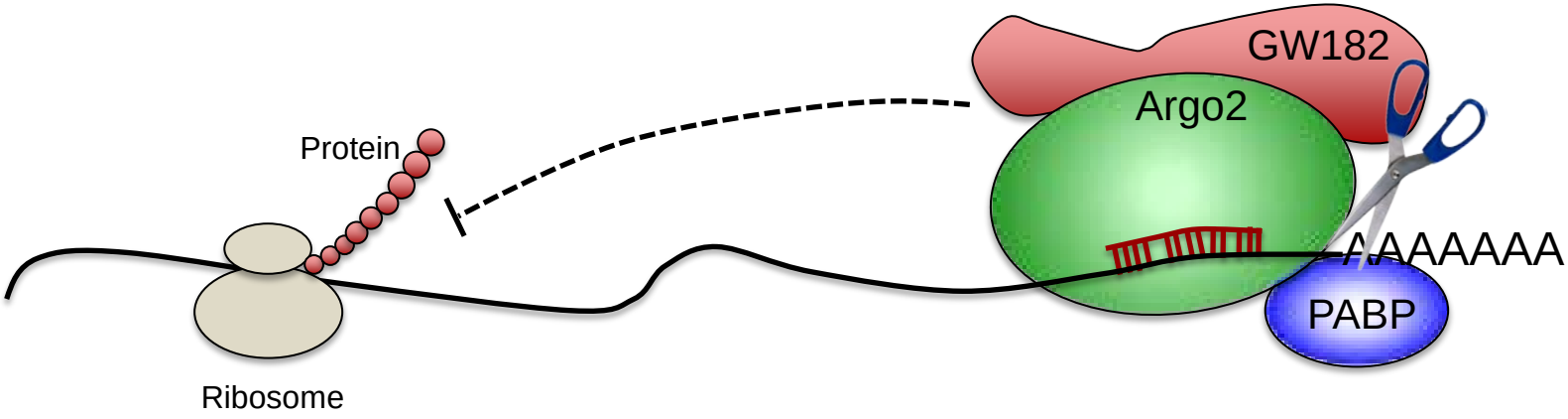
MICRORNAS IN NORMAL AND FAILING HEARTS

Gerald W Dorn II, MD



FINANCIAL DISCLOSURE:
No conflicts. No unlabeled drug use. Research funded by NIH/NHLBI

Center for Pharmacogenomics

Washington University in St. Louis School of Medicine

ARTICLES

nature structural & molecular biology

Purified Argonaute2 and an siRNA form recombinant human RISC

Fabiola V Rivas[1,3], Niraj H Tolia[1–3], Ji-Joon Song[1–3], Juan P Aragon[1], Jidong Liu[1], Gregory J Hannon[1] & Leemor Joshua-Tor[1,2]

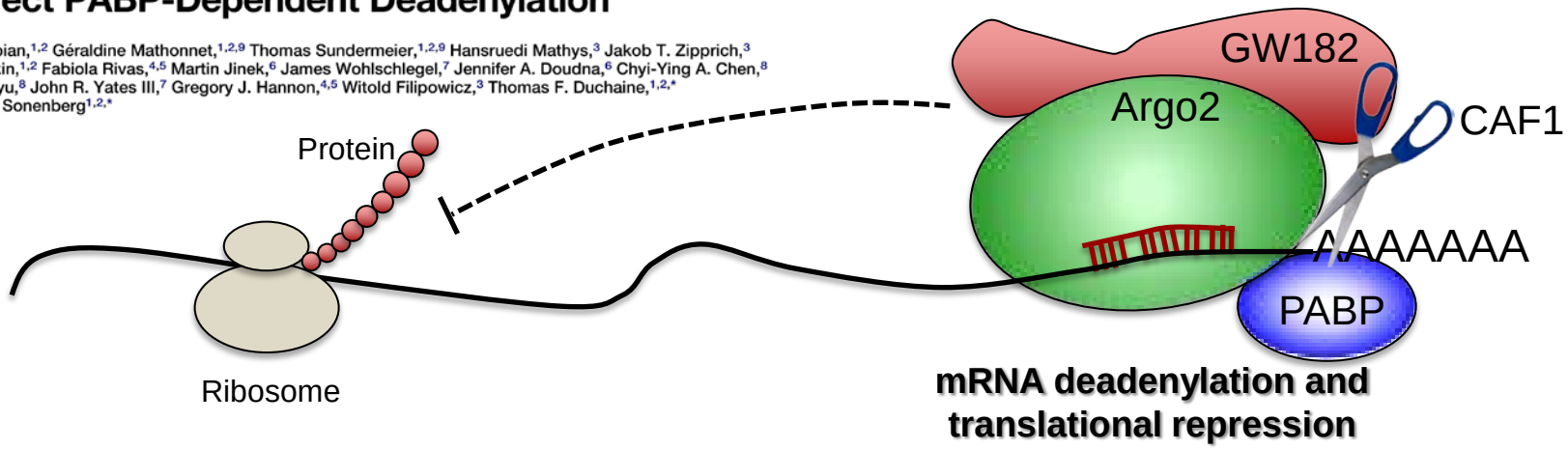
v.nature.com/nsmb

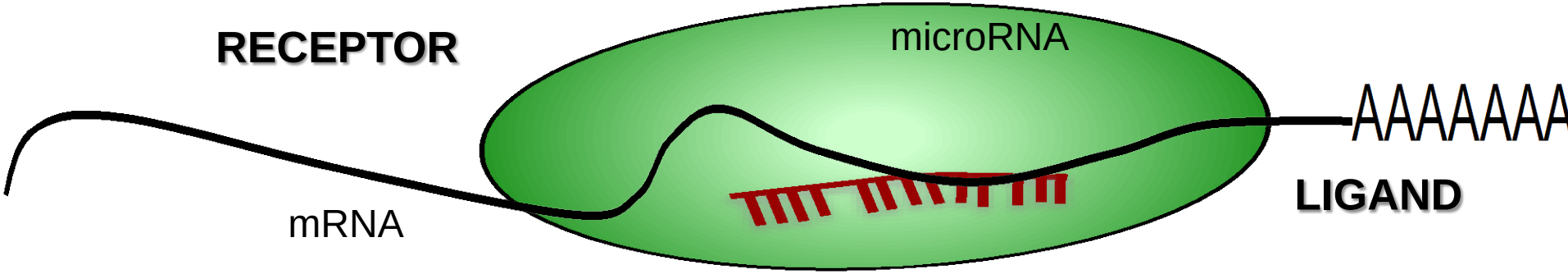
Cell PRESS

Molecular Cell
Article

Mammalian miRNA RISC Recruits CAF1 and PABP to Affect PABP-Dependent Deadenylation

Marc R. Fabian,[1,2] Géraldine Mathonnet,[1,2,9] Thomas Sundermeier,[1,2,9] Hansruedi Mathys,[3] Jakob T. Zipprich,[3] Yuri V. Svitkin,[1,2] Fabiola Rivas,[4,5] Martin Jinek,[6] James Wohlschlegel,[7] Jennifer A. Doudna,[6] Chyi-Ying A. Chen,[8] Ann-Bin Shyu,[8] John R. Yates III,[7] Gregory J. Hannon,[4,5] Witold Filipowicz,[3] Thomas F. Duchaine,[1,2,*] and Nahum Sonenberg[1,2,*]

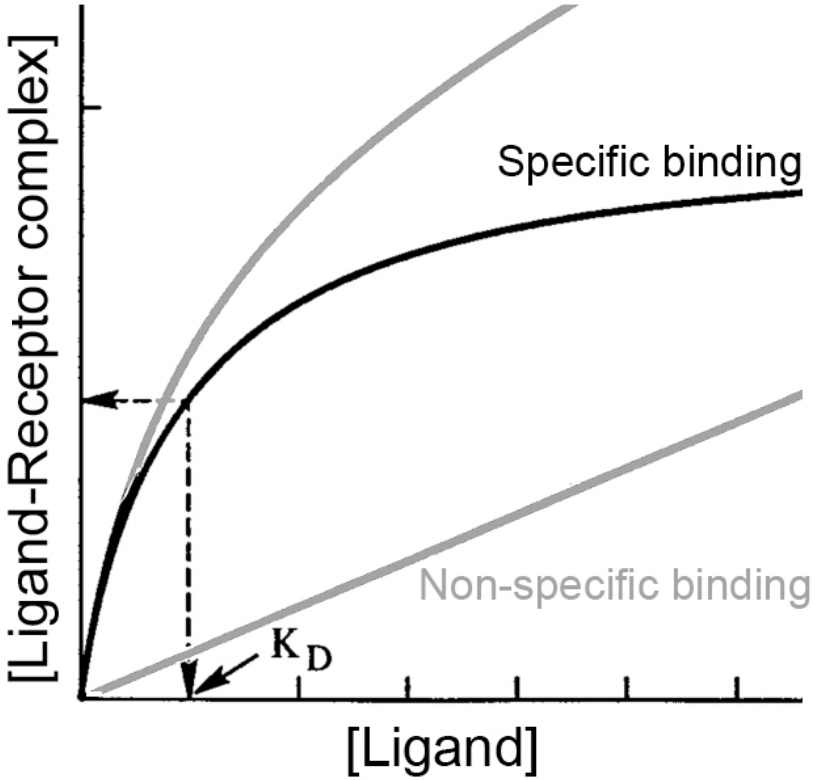




Watson-Crick pairing

binding energy

$$[miR] + [mRNA] \leftrightarrow [duplex]$$



Watson-Crick pairing

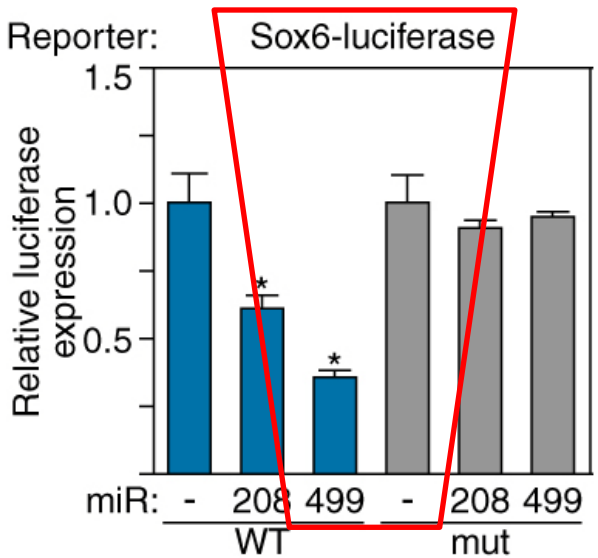
Cell PRESS

Developmental Cell
Article

A Family of microRNAs Encoded by Myosin Genes Governs Myosin Expression and Muscle Performance

Eva van Rooij,[1,3] Daniel Quiat,[1] Brett A. Johnson,[1] Lillian B. Sutherland,[1] Xiaoxia Qi,[1] James A. Richardson,[1,2] Robert J. Kelm Jr.,[4] and Eric N. Olson[1,*]

MyomiRs Directly Repress Predicted Target Genes



miR-499 5'-UUAAGACUUGCAGUGAUGUUU-3'

3'-AAUUCUGAAGACGACUACAUU-5'
3'-UAUUCUGAACAUUCUGUAGAU-5'
3'-AAUUCUGAAAGUUUUAUAAUU-5'
3'-GAUUCUGAACGUCACAGAGGA-5'
3'-AAUUCUGACUUACAGUCCCAA-5'

Sox6 (human)

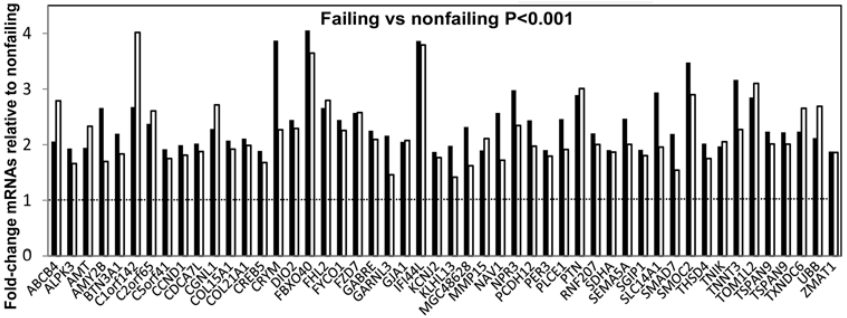
Highly variable

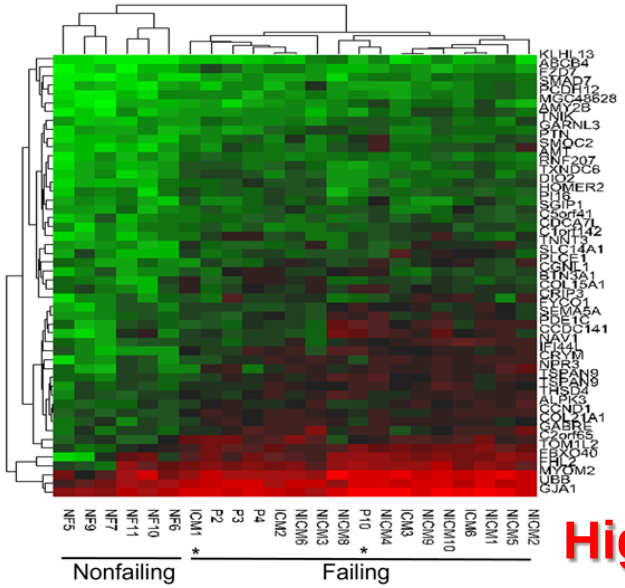
binding energy

[miR] + [mRNA] ↔ [duplex]

Ligand (mRNA) concentration

Cardiac mRNA levels/nonfailing





Highly variable

Reciprocal Regulation of Myocardial microRNAs and Messenger RNA in Human Cardiomyopathy and Reversal of the microRNA Signature by Biomechanical Support

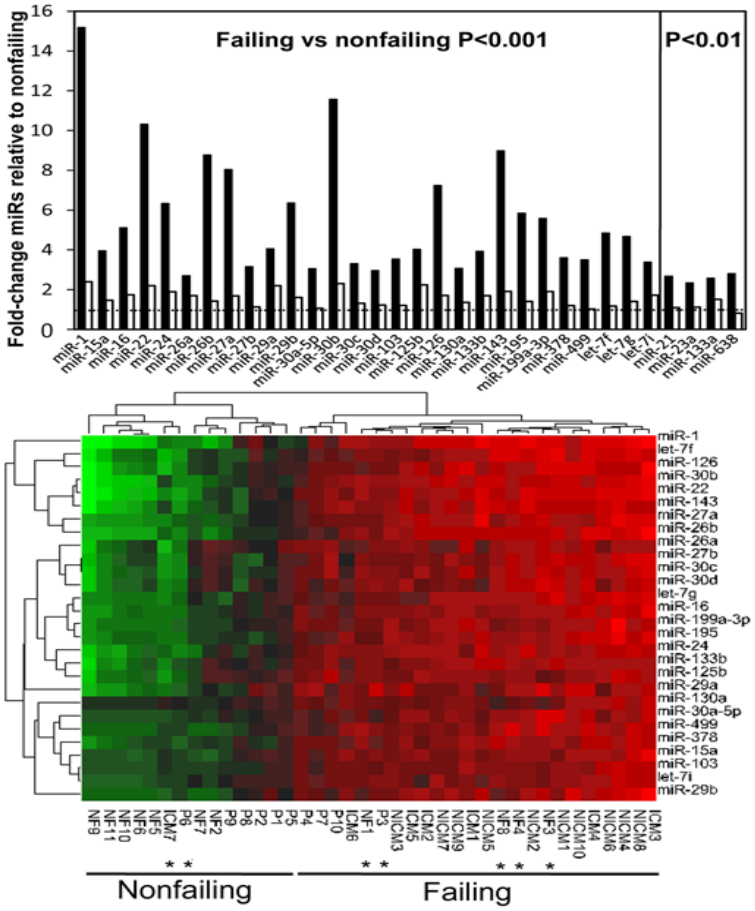
Scot J. Matkovich, PhD; Derek J. Van Booven, BS; Keith A. Youker, PhD;
Guillermo Torre-Amione, MD, PhD; Abhinav Diwan, MD;
William H. Eschenbacher; Lisa E. Dorn; Mark A. Watson, MD, PhD;
Kenneth B. Margulies, MD; Gerald W. Dorn II, MD

Circulation, 119:1263-71, 2009

[miR] + [mRNA] ↔ [duplex]

Receptor (miR) concentration

Cardiac miR levels/nonfailing



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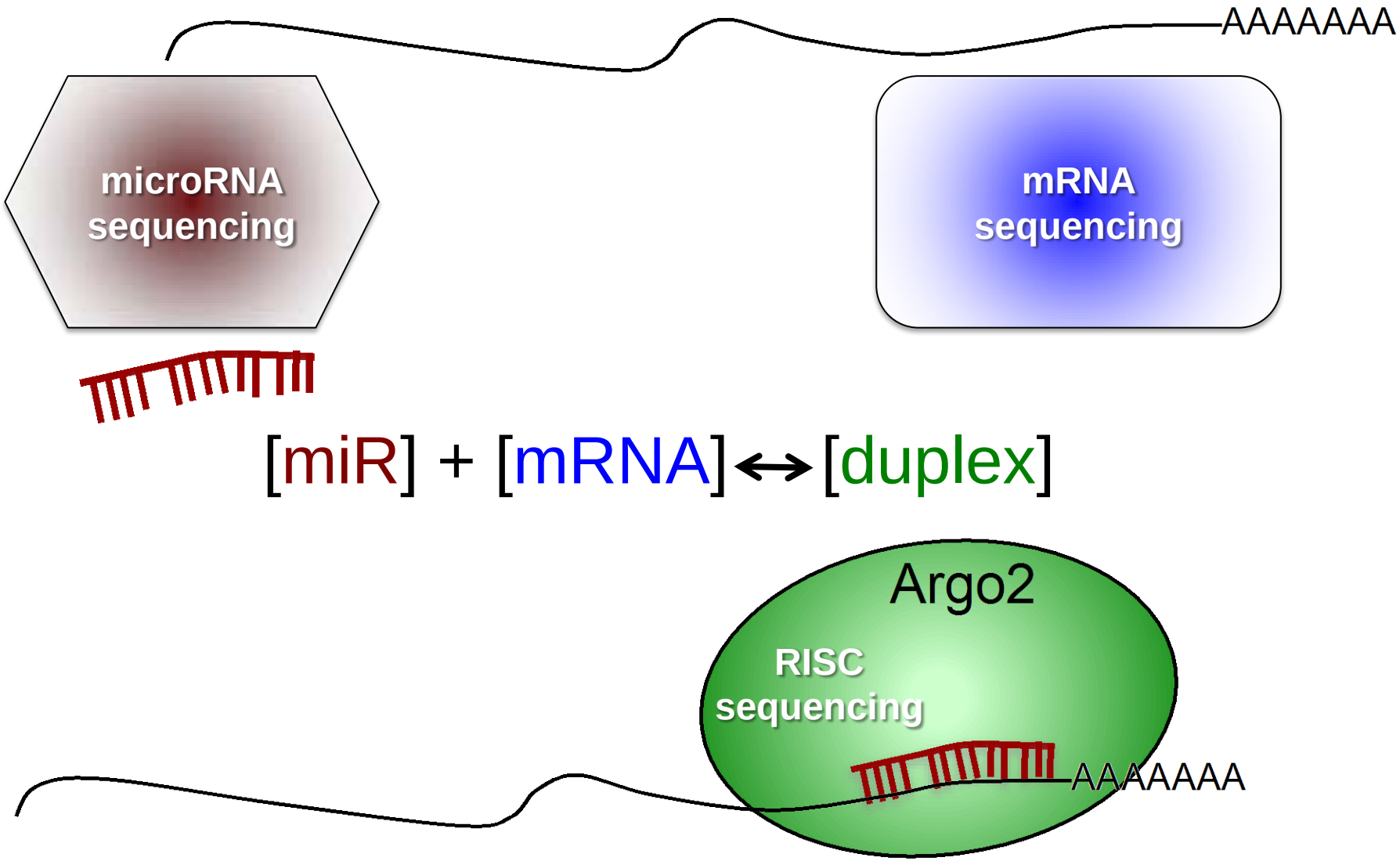
Circulation, 119:1263-71, 2009

Highly variable

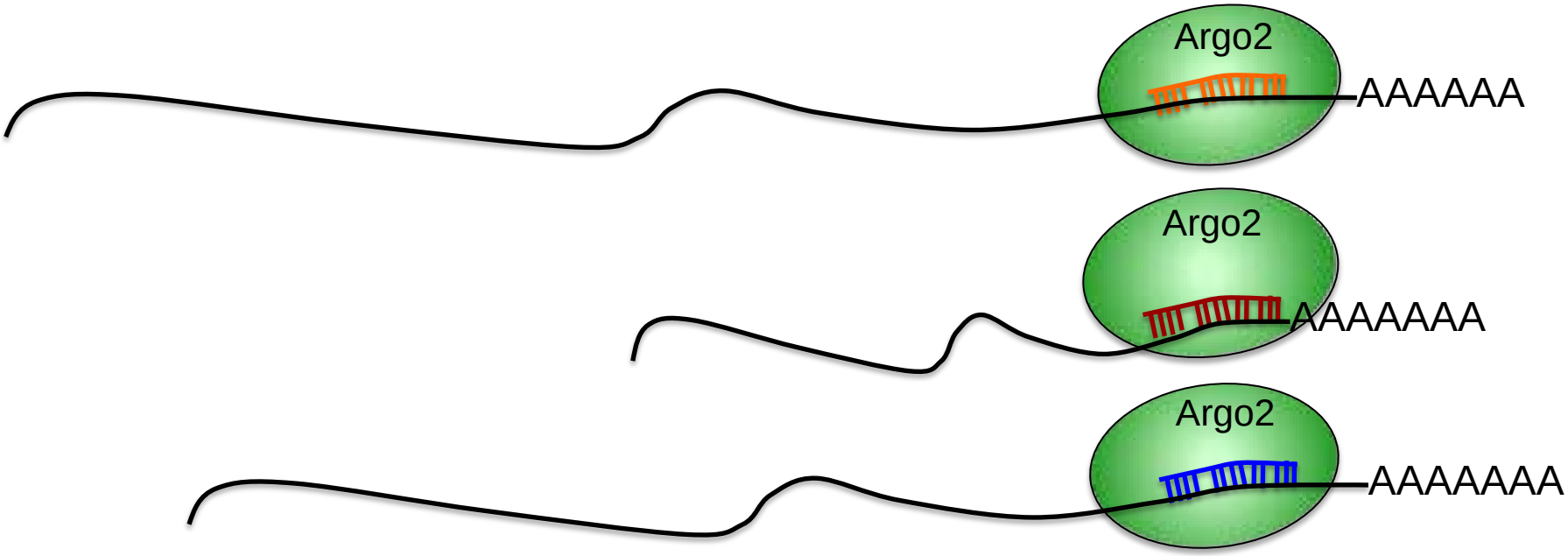
[miR] + [mRNA] ↔ [duplex]

Deconvolution strategy:



RNA sequencing of Argo 2 immunoprecipitates identifies the

RISCome: the total population of mRNAs targeted by the miRs expressed under the conditions of the experiment



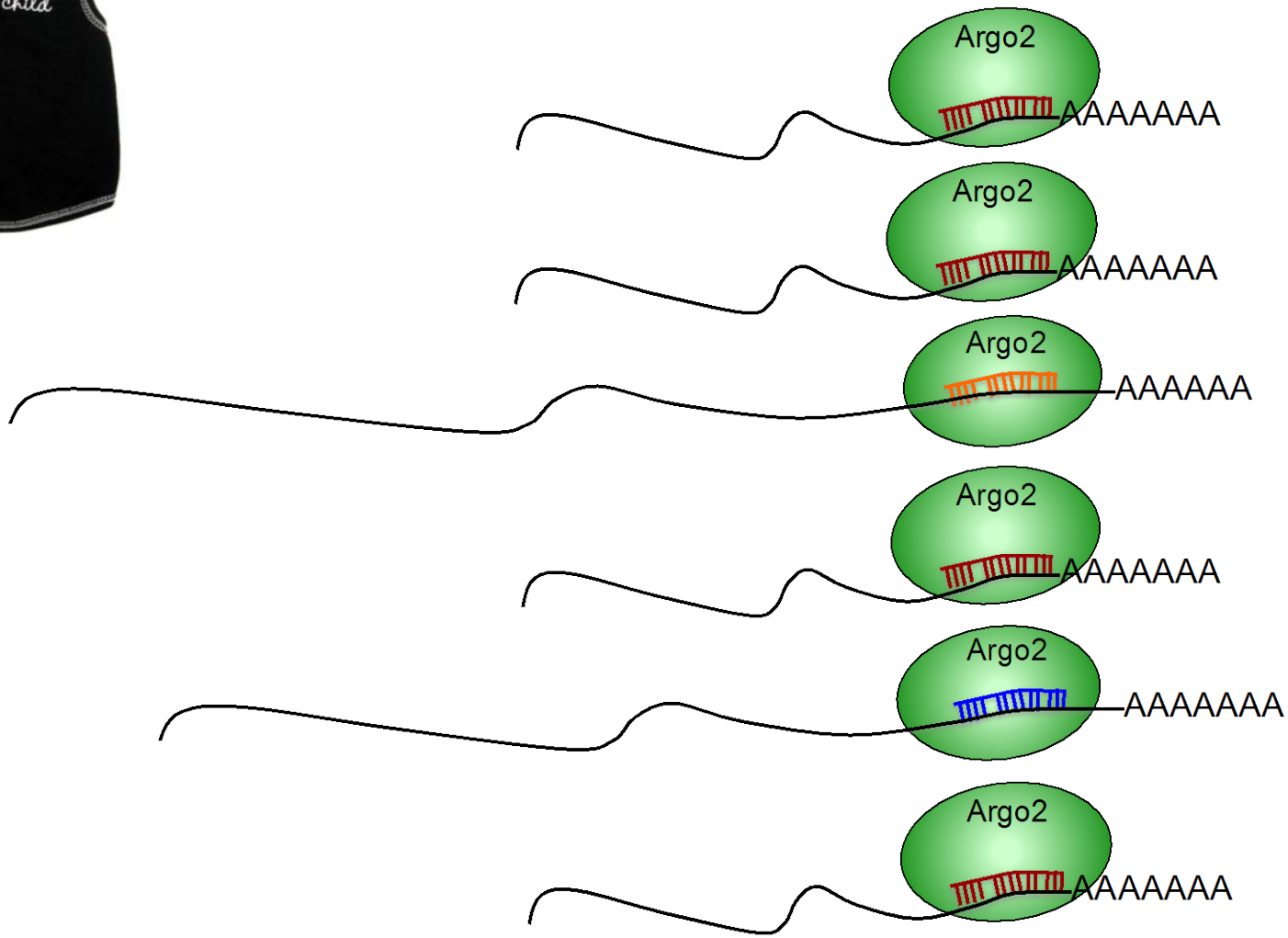
RISC RNA Sequencing for Context-Specific Identification of In Vivo MicroRNA Targets

Scot J. Matkovich, Derek J. Van Booven, William H. Eschenbacher, Gerald W. Dorn II

Circ Res, 108:18-26, 2011

ALL miR-mRNA complexes vs MY FAVORITE miR-RNA duplex

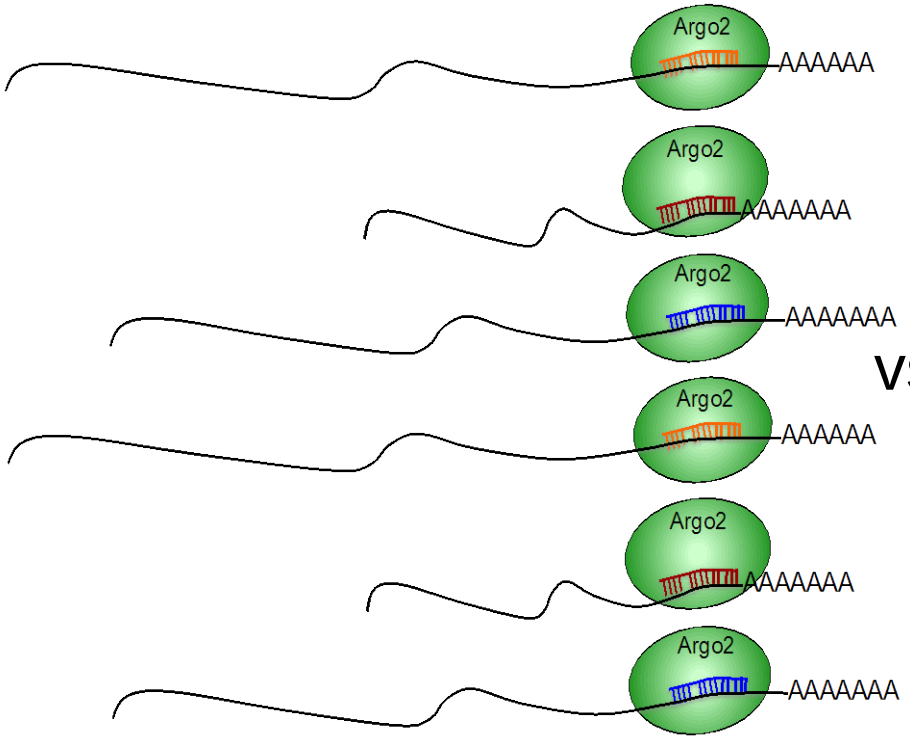
RISC Programming: *forced miR expression to increase the proportion of its mRNA targets in the RISCome.*



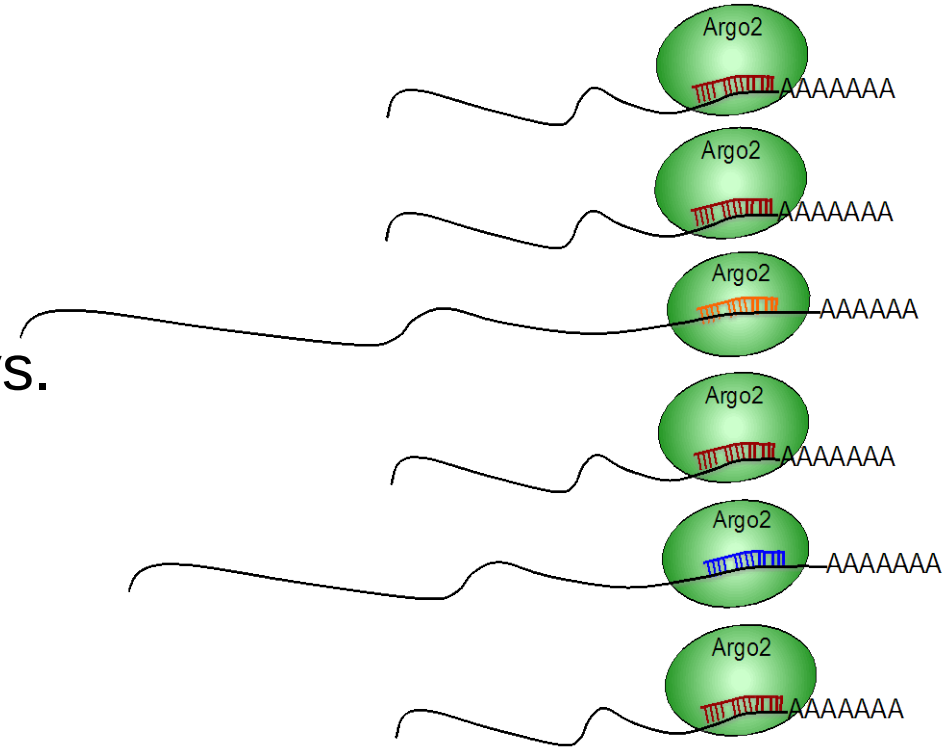
NTG **miR-TG**

Unprogrammed RISCome

Red miR-programmed RISCome



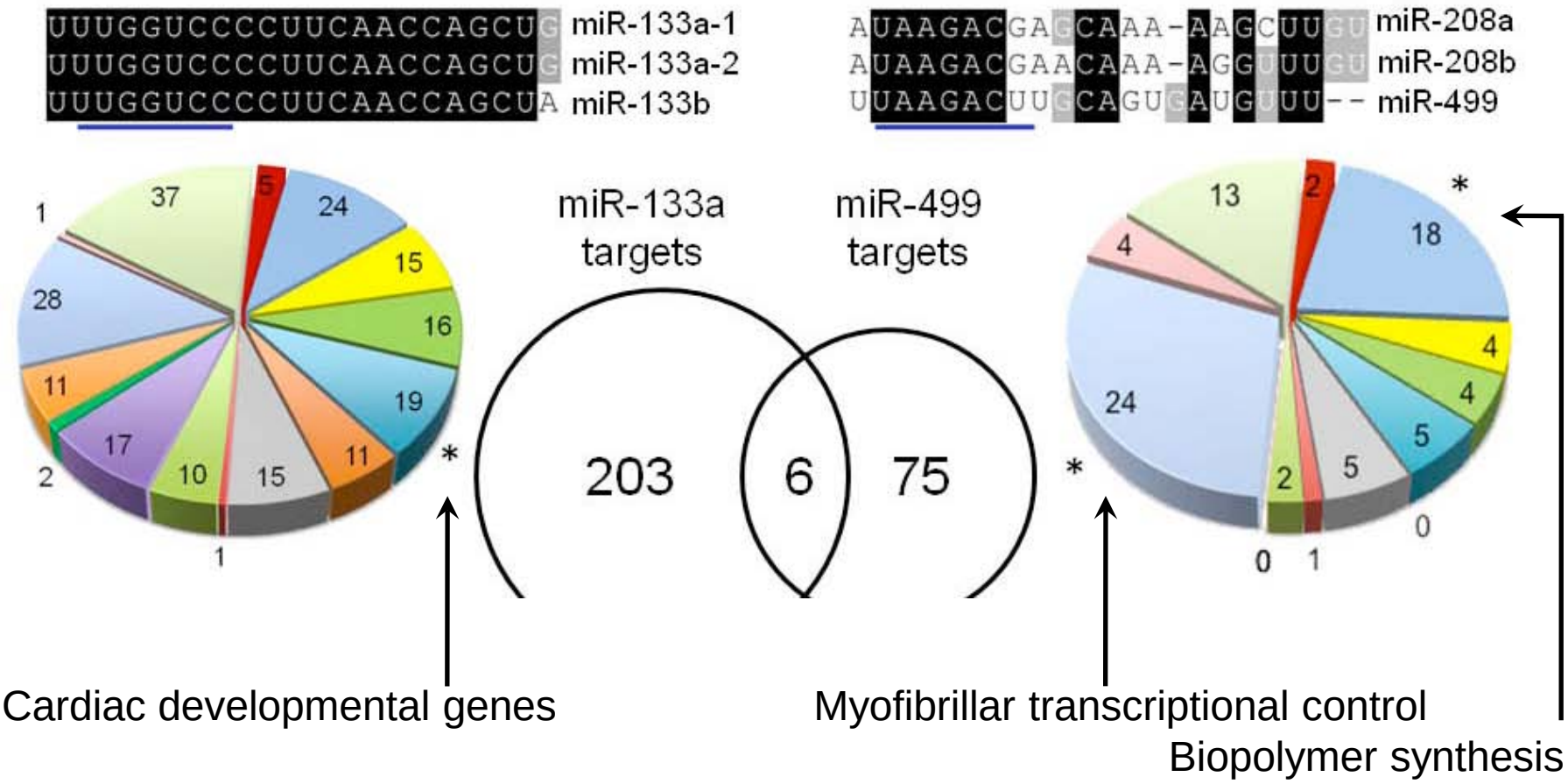
vs.



$$\frac{\text{Red miR-associated mRNA}}{\text{Total miR-associated mRNA}} = 33\%$$

$$\frac{\text{Red miR-associated mRNA}}{\text{Total miR-associated mRNA}} = 66\%$$

Programmed miR-133a and miR-499 mouse heart RISComes reveal miR-specific in vivo cardiac mRNA targets



Circ Res, 108:18-26, 2011

MyomiR miR-499: Orphan miR from a discarded gene

Cell PRESS

Developmental Cell
Article

A Family of microRNAs Encoded by Myosin Genes Governs Myosin Expression and Muscle Performance

Eva van Rooij,[1,3] Daniel Quiat,[1] Brett A. Johnson,[1] Lillian B. Sutherland,[1] Xiaoxia Qi,[1] James A. Richardson,[1,2] Robert J. Kelm Jr.,[4] and Eric N. Olson[1,*]

1. miR-499 is expressed at high levels in myocardium
2. miR-499 is encoded within an intron of *Myh7b*
3. Myh7b is barely detectable in myocardium (nonsense-mediated decay)

Conclusion: cardiac expression of *Myh7b*/miR-499 gene is just for miR-499