MicroRNA reprogramming in cancer: Mechanisms and therapeutic opportunities

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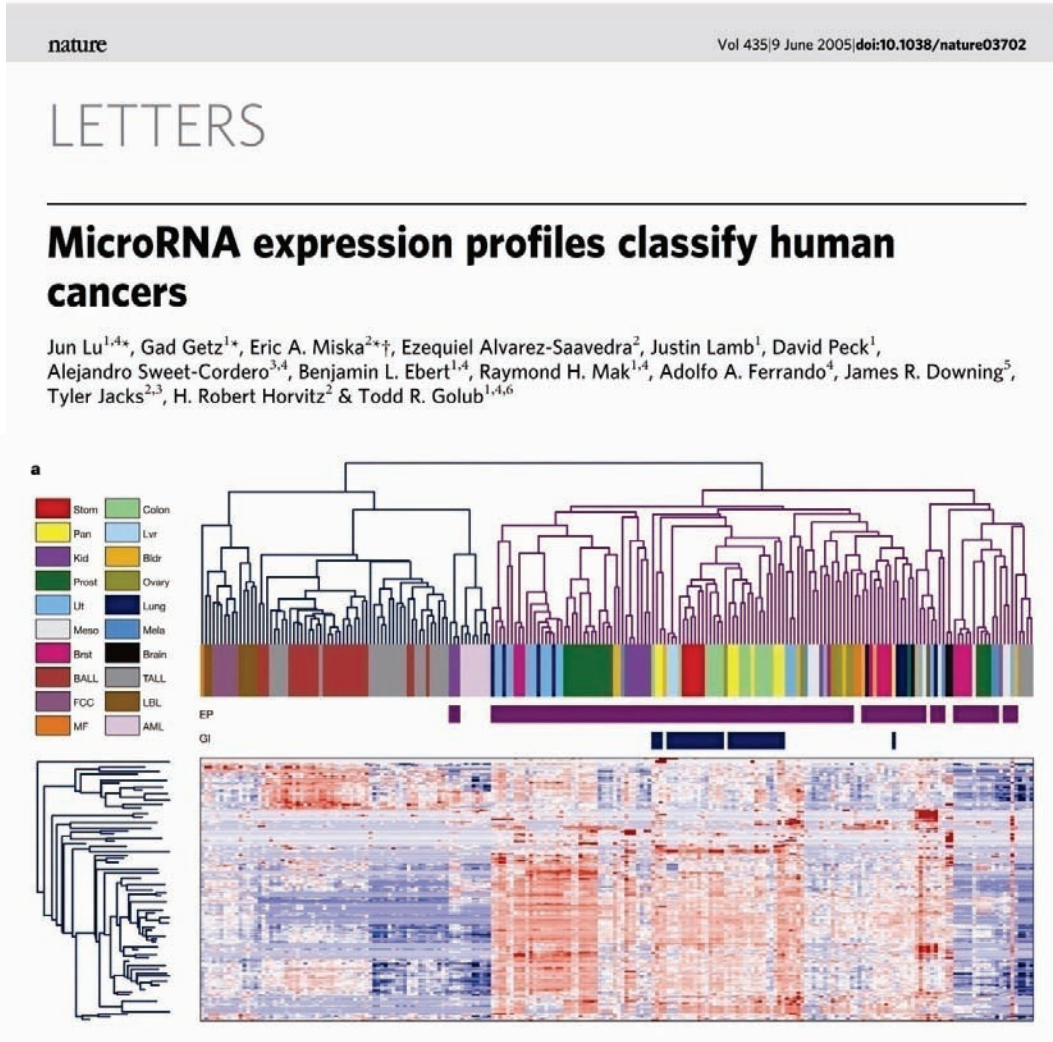
Abnormal microRNA expression is a ubiquitous feature of cancer cells…



nature Vol 435|9 June 2005|doi:10.1038/nature03702

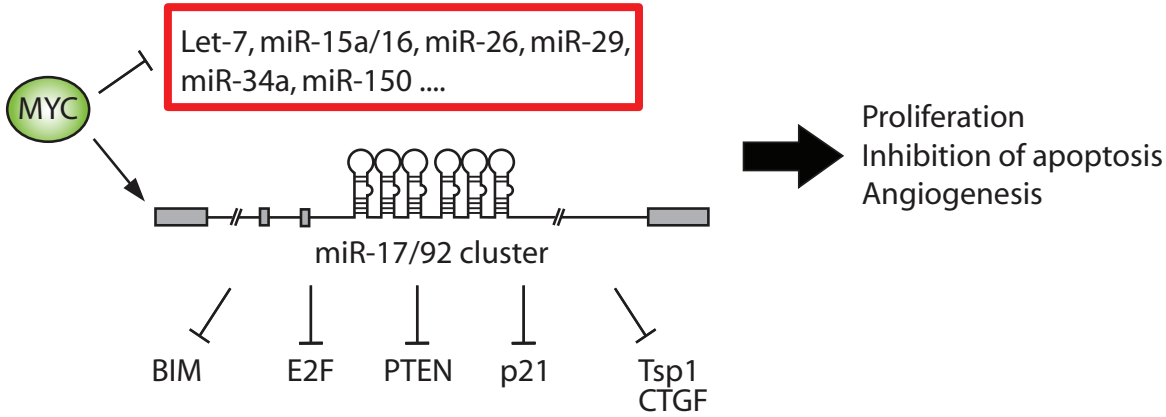
LETTERS

MicroRNA expression profiles classify human cancers

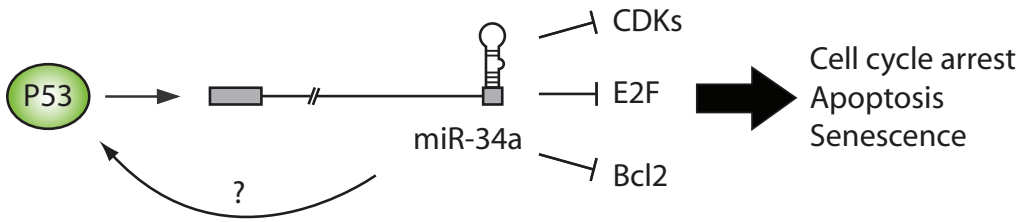
Jun Lu[1,4]*, Gad Getz[1]*, Eric A. Miska[2]*†, Ezequiel Alvarez-Saavedra[2], Justin Lamb[1], David Peck[1], Alejandro Sweet-Cordero[3,4], Benjamin L. Ebert[1,4], Raymond H. Mak[1,4], Adolfo A. Ferrando[4], James R. Downing[5], Tyler Jacks[2,3], H. Robert Horvitz[2] & Todd R. Golub[1,4,6]

What strategies are effective for identifying miRNAs that drive tumorigenesis?

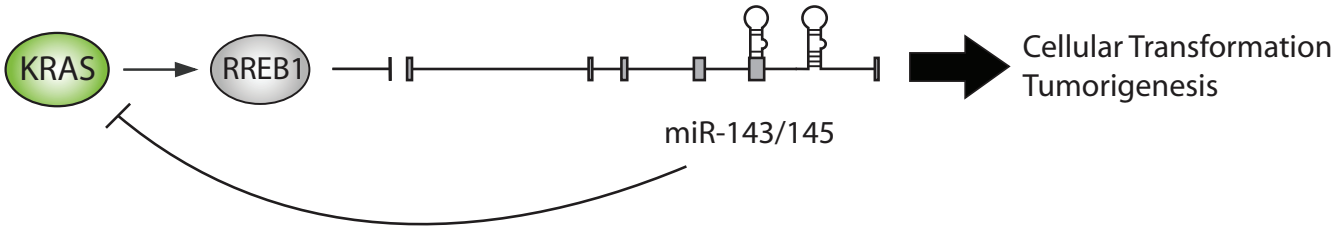
MicroRNAs function as key components of oncogenic and tumor suppressor pathways



O'Donnell *et al. Nature* 2005
Chang *et al. Nat Genetics* 2008
Chang *et al. PNAS* 2009
Kota *et al. Cell* 2010



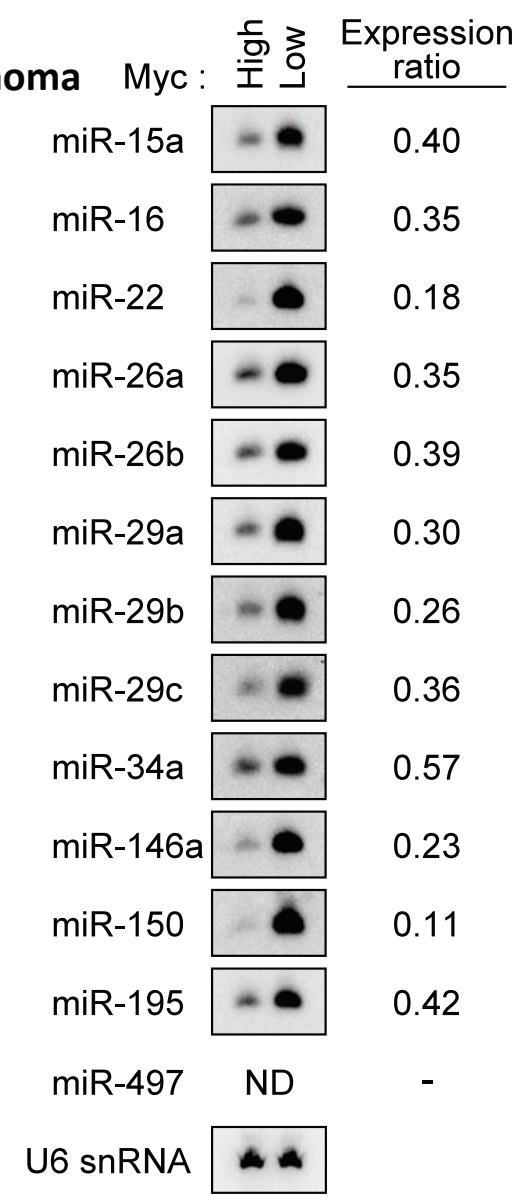
Chang *et al. Mol Cell* 2007



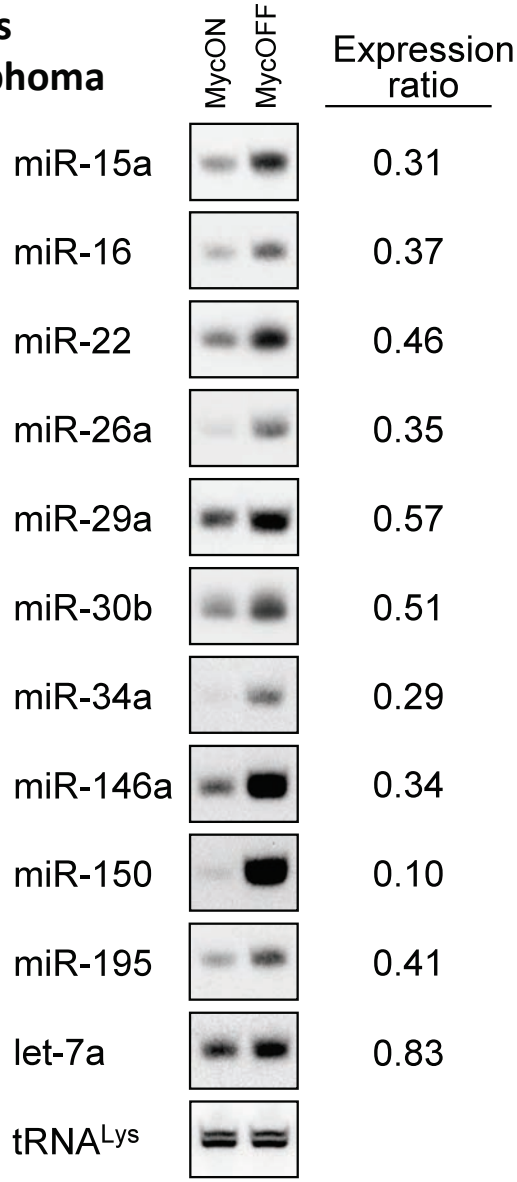
Kent *et al. Genes Dev* 2010

Widespread repression of miRNAs by Myc

P493-6 cells
***In vitro* B lymphoma**



MycER tumors
***In vivo* B lymphoma**

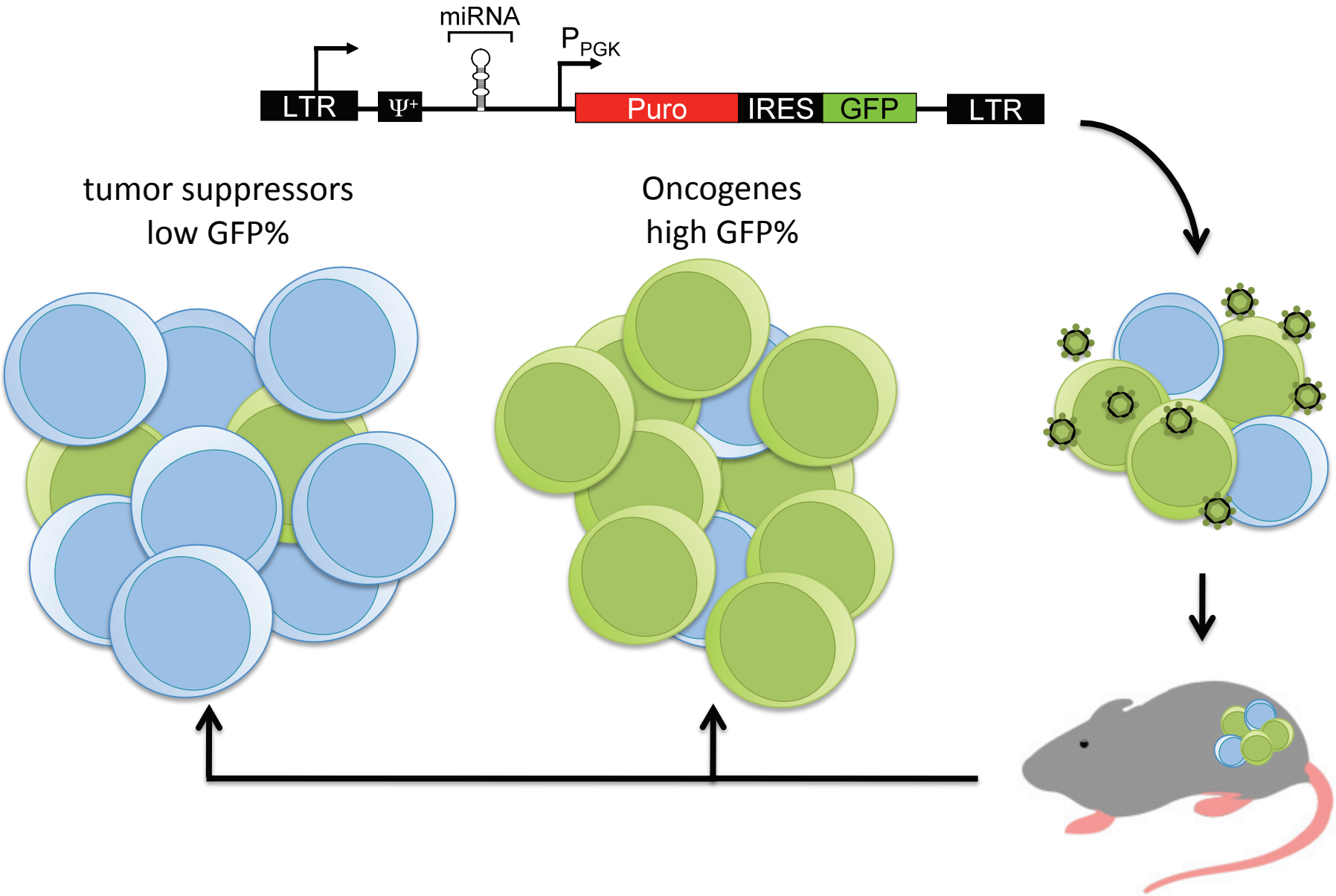


Chang *et al. Nature Genetics*, 2008

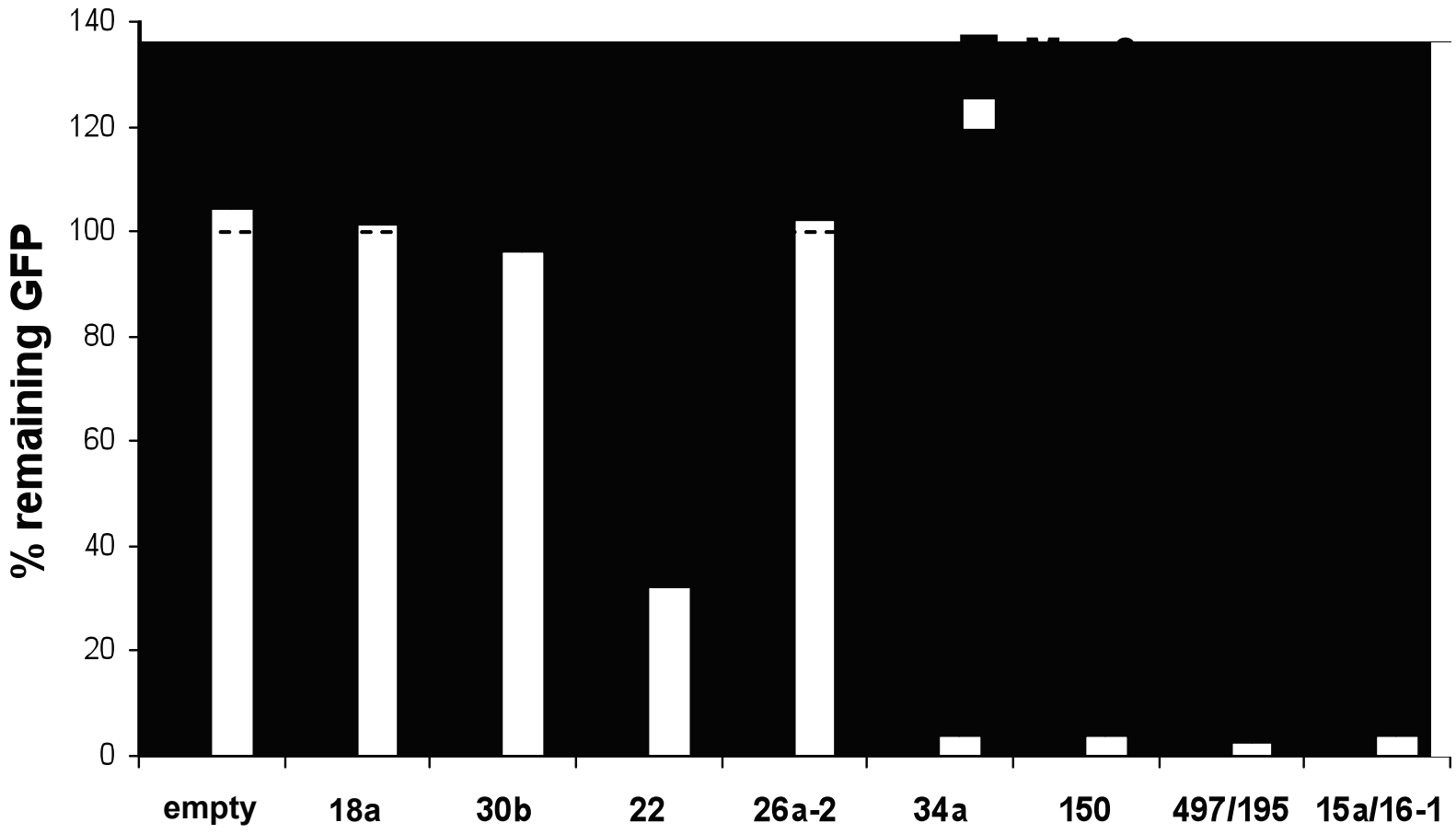
Does Myc-mediated miRNA repression contribute to tumorigenesis?

Tsung-Cheng Chang

in vivo lymphoma selection model

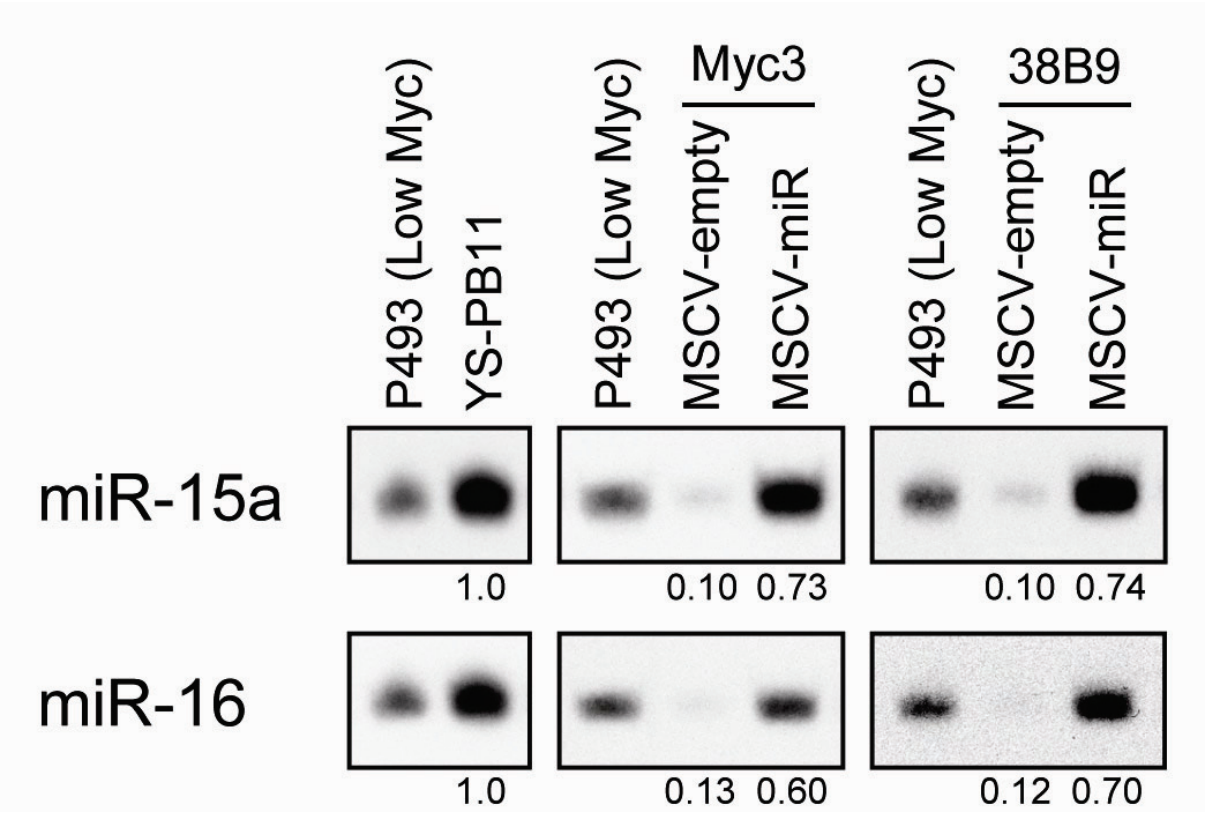


Expression of Myc-repressed microRNAs inhibits tumorigenesis



Chang *et al. Nature Genetics*, 2008

Could miRNA replacement provide a tumor-specific therapeutic strategy?



Sub-physiologic expression potently suppresses tumorigenesis

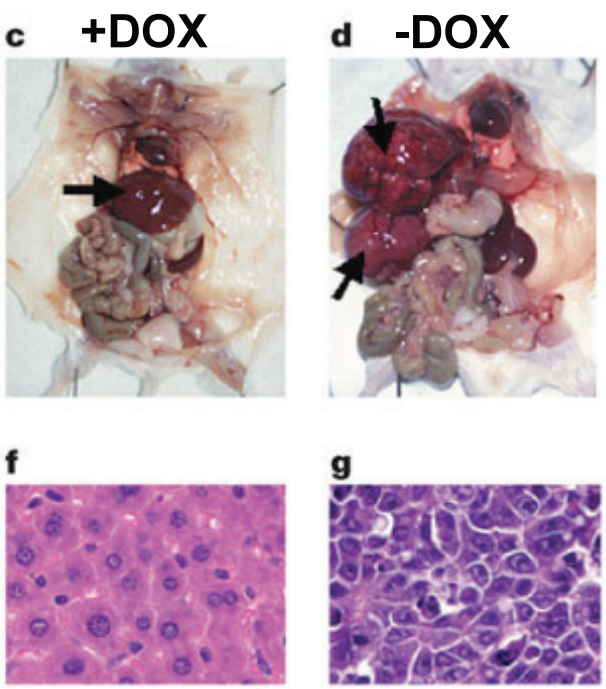
Could miRNA replacement provide a tumor-specific therapeutic strategy?

Janaiah Kota

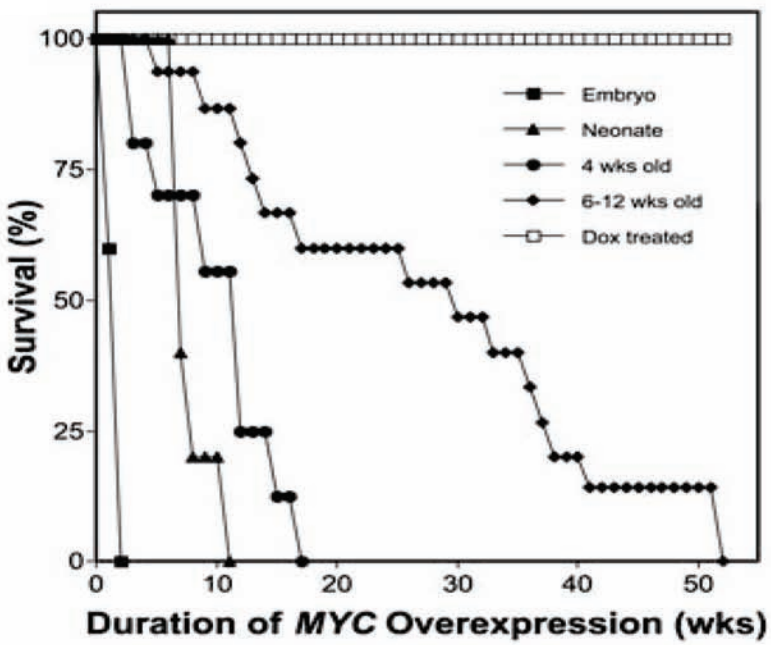
Raghu Chivukula

Inducible model of Myc-driven hepatocellular carcinoma

Tet-*O-MYC* x LAP-tTA



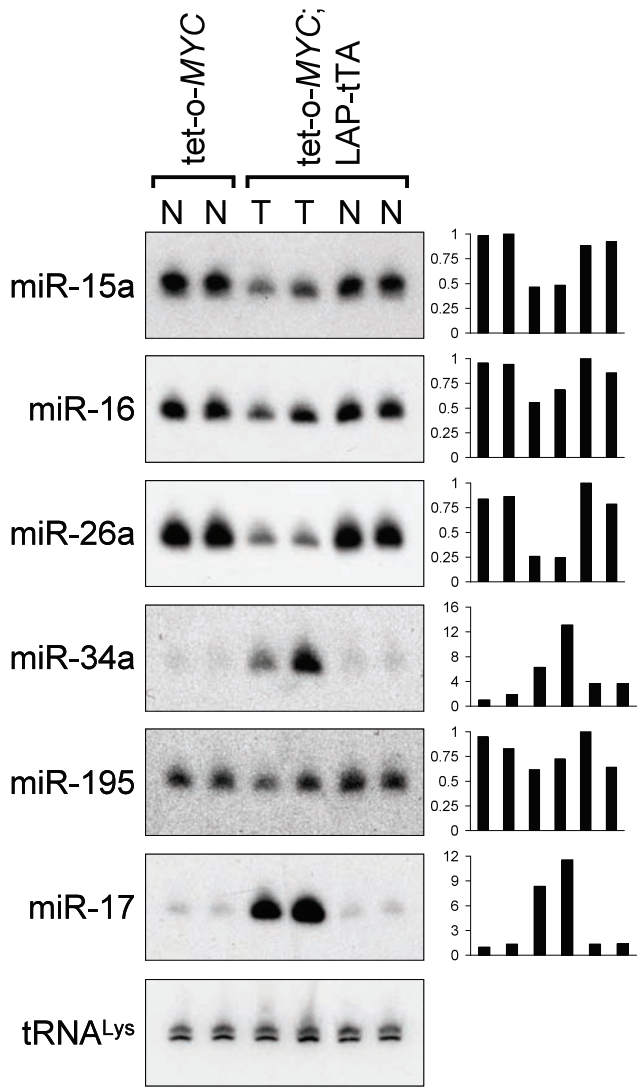
Developmental context determines latency of liver tumorigenesis

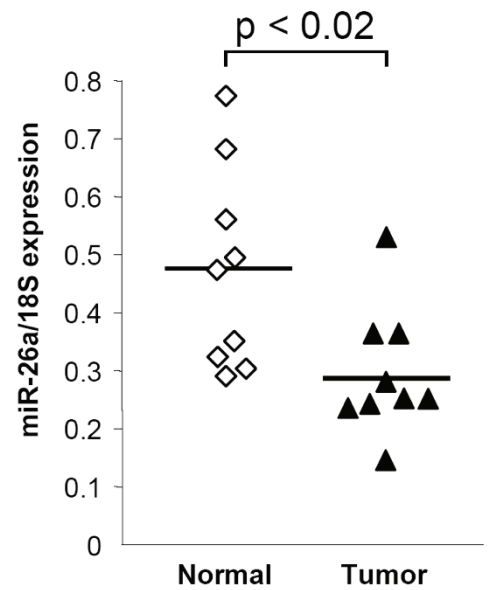


Shachaf *et al*, *Nature*, 2004

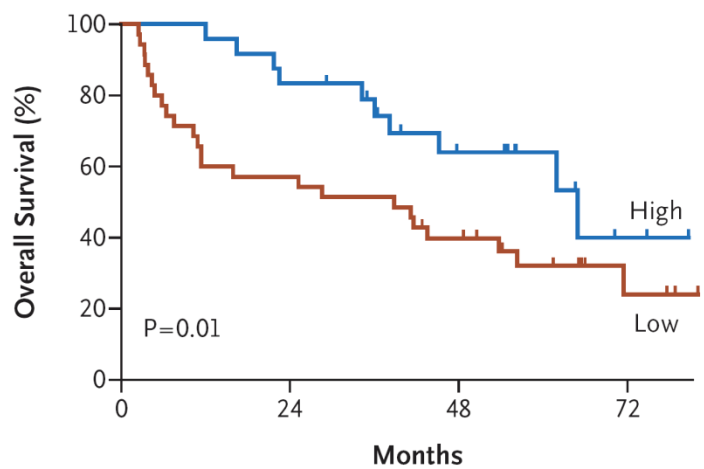
Beer *et al*, *PLoS Biol*, 2004

Downregulation of anti-tumorigenic miRNAs in murine and human liver tumors



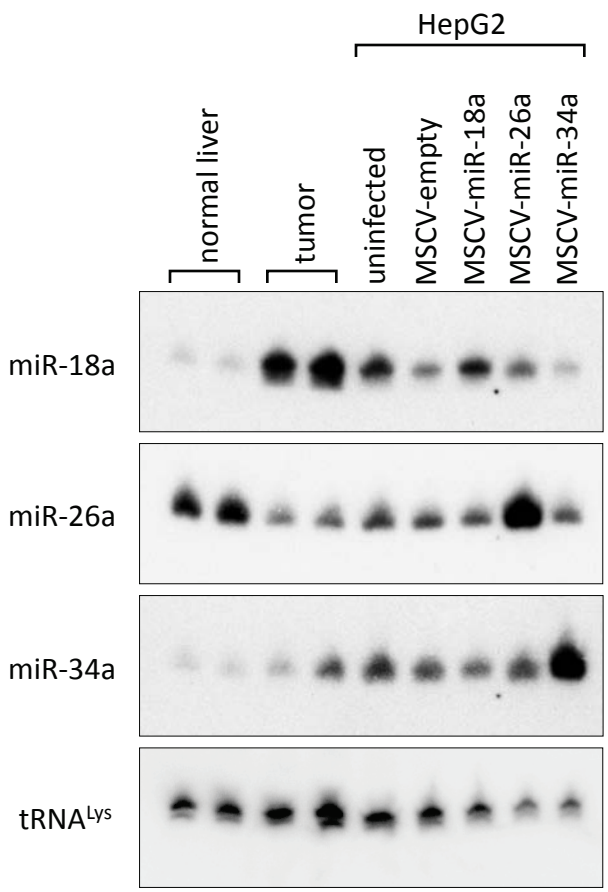


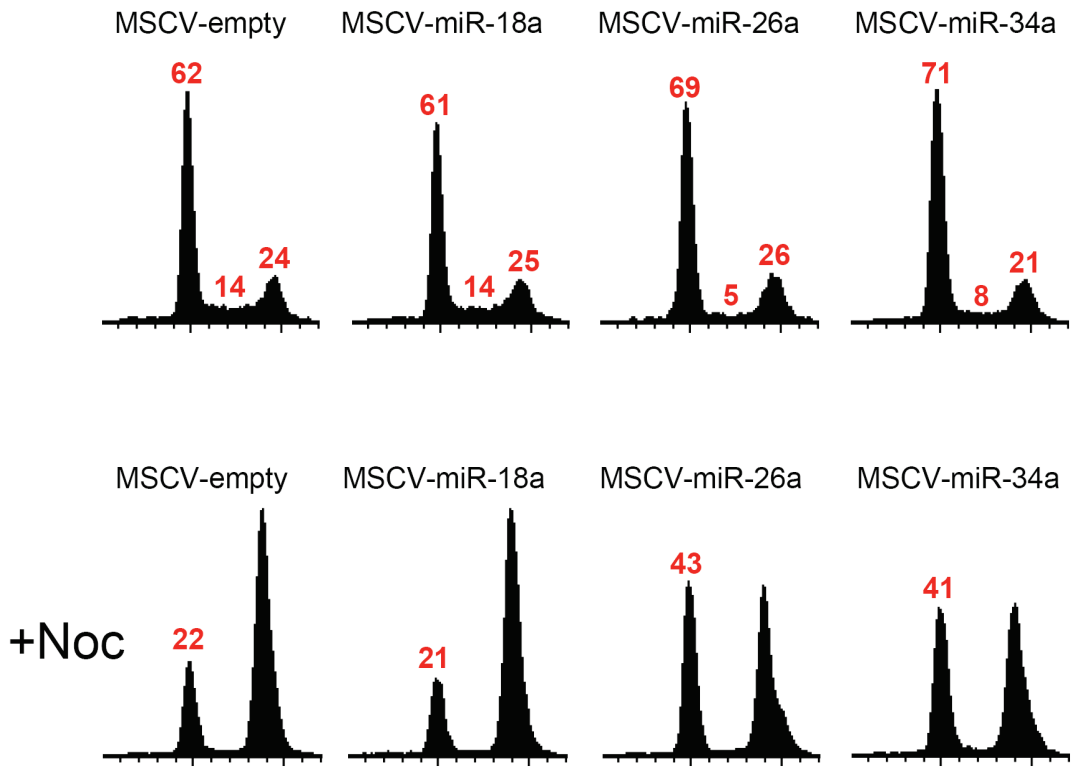
Ji *et al.*, *NEJM*, 2009



Kota *et al. Cell,* 2009

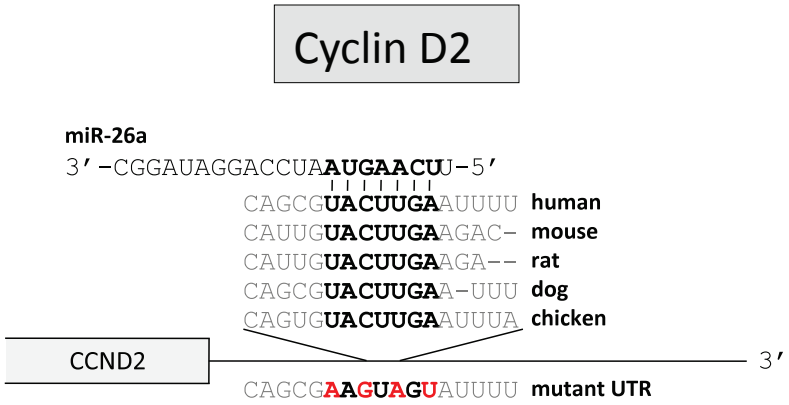
miR-26a induces a G1 arrest in human HCC cells

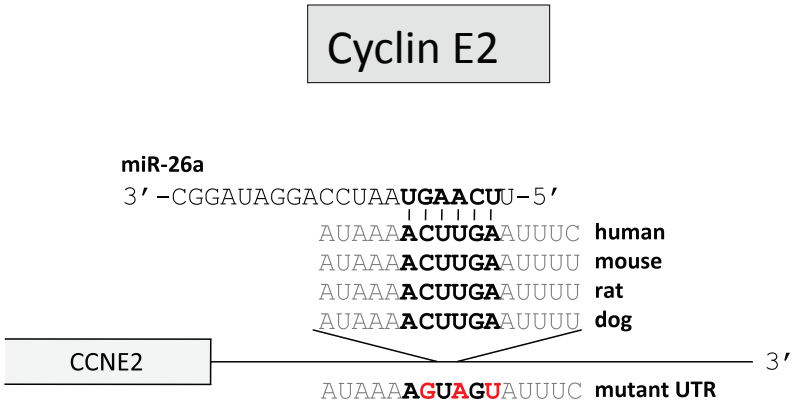


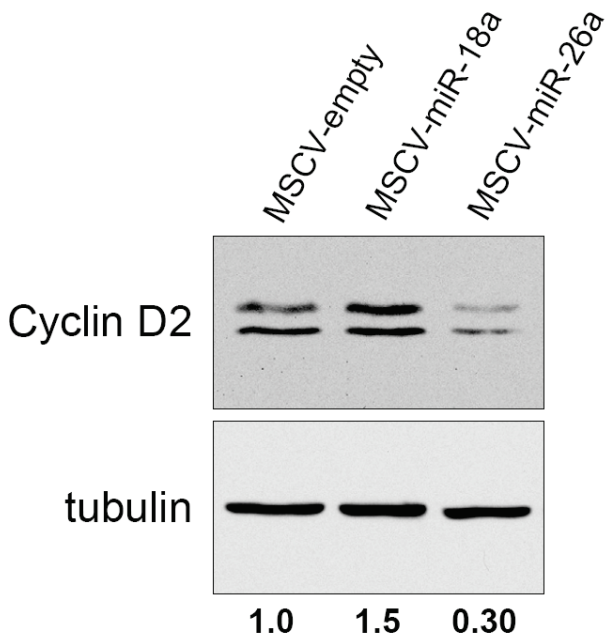


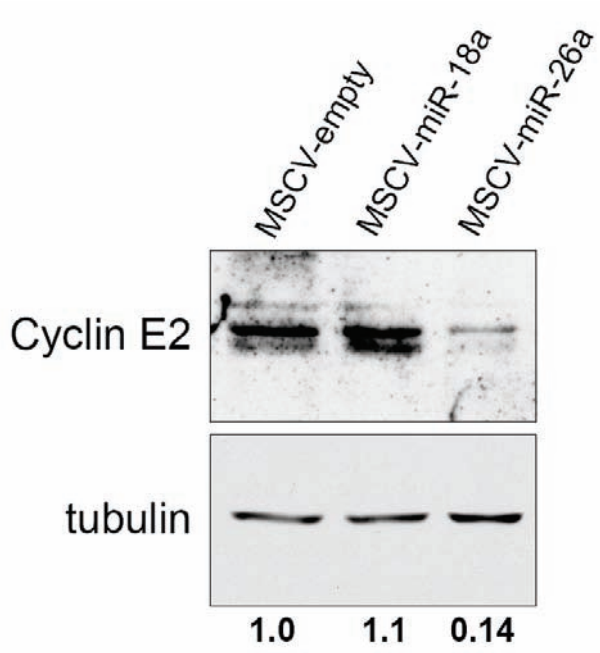
Kota *et al. Cell,* 2009

miR-26a represses multiple G1 cyclins









Kota *et al. Cell,* 2009

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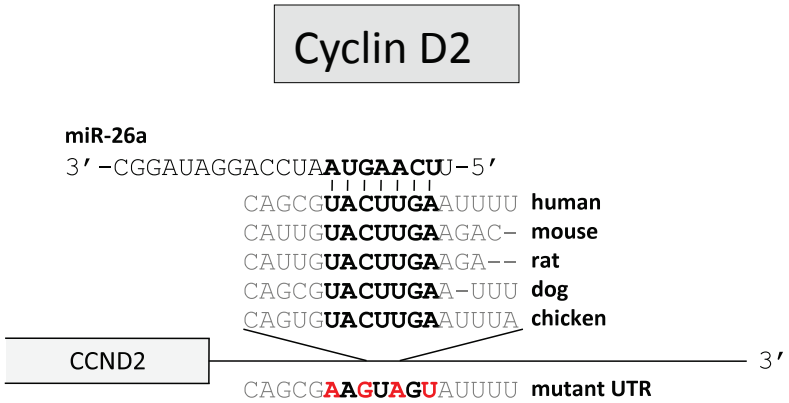
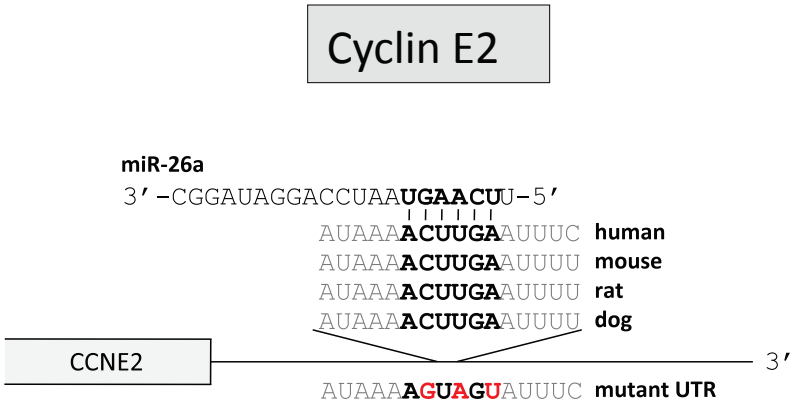
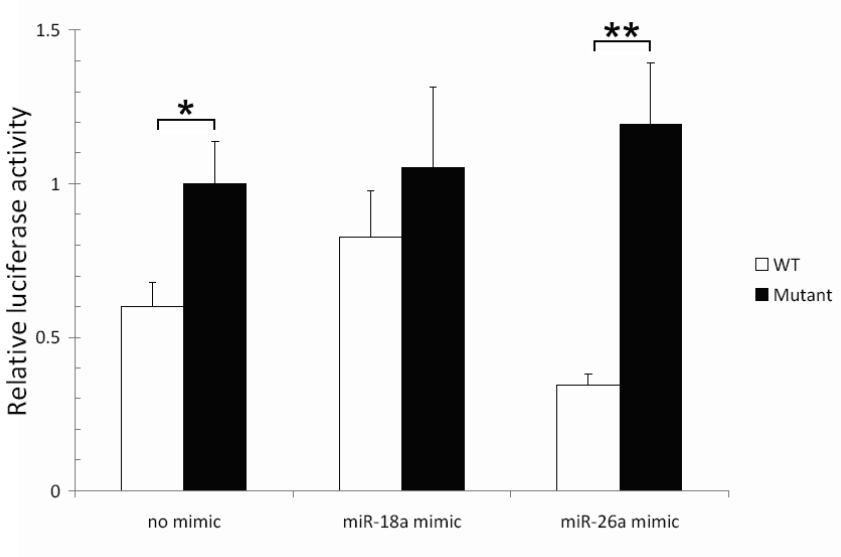
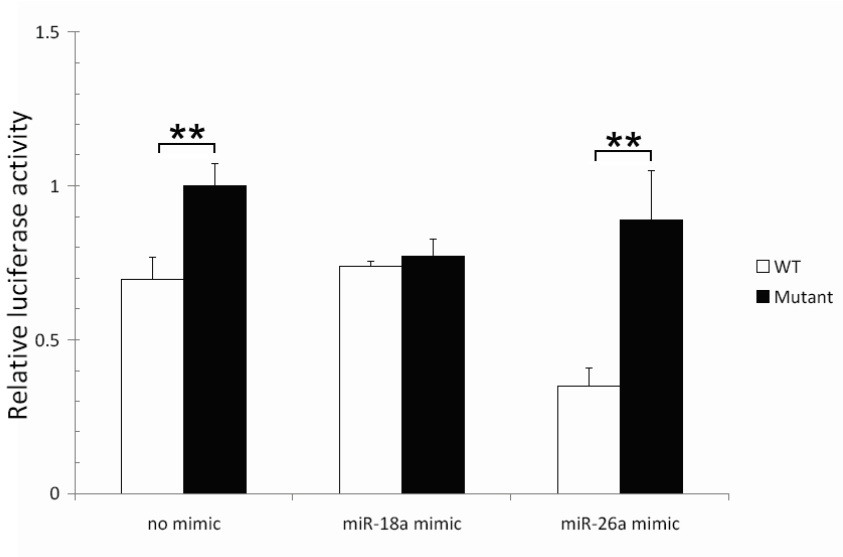


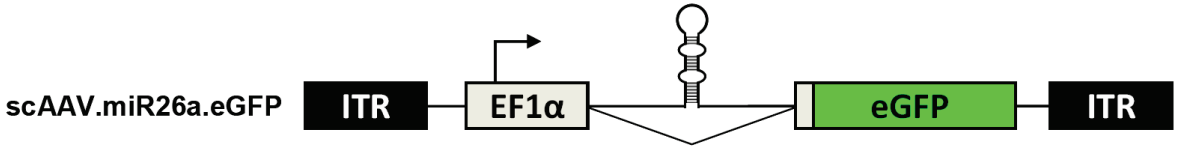


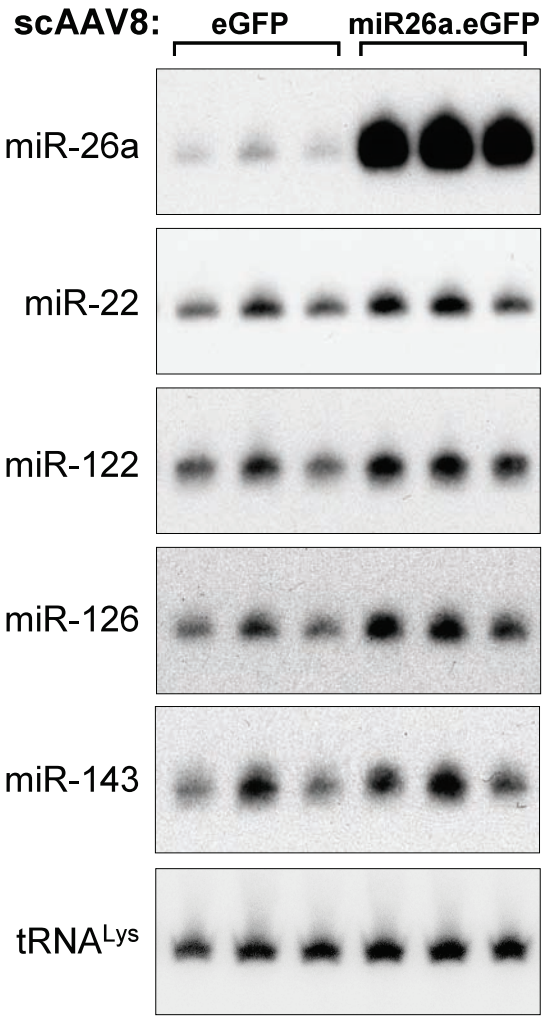


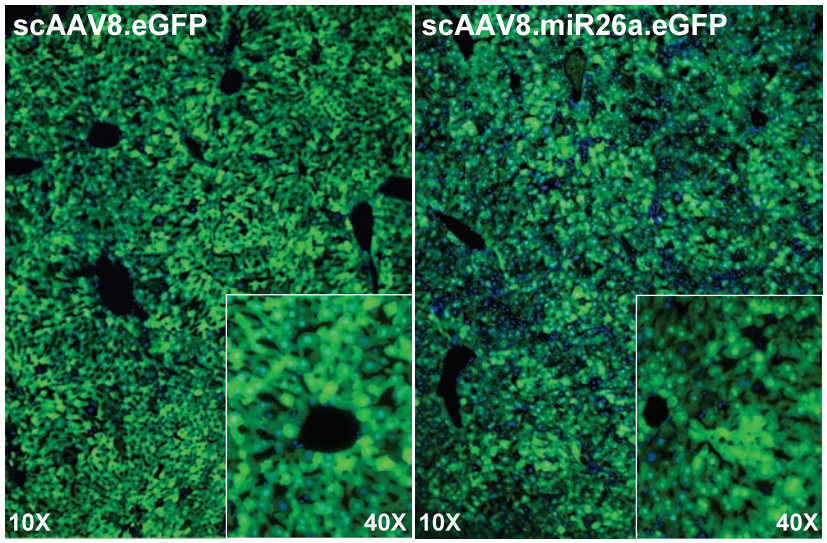


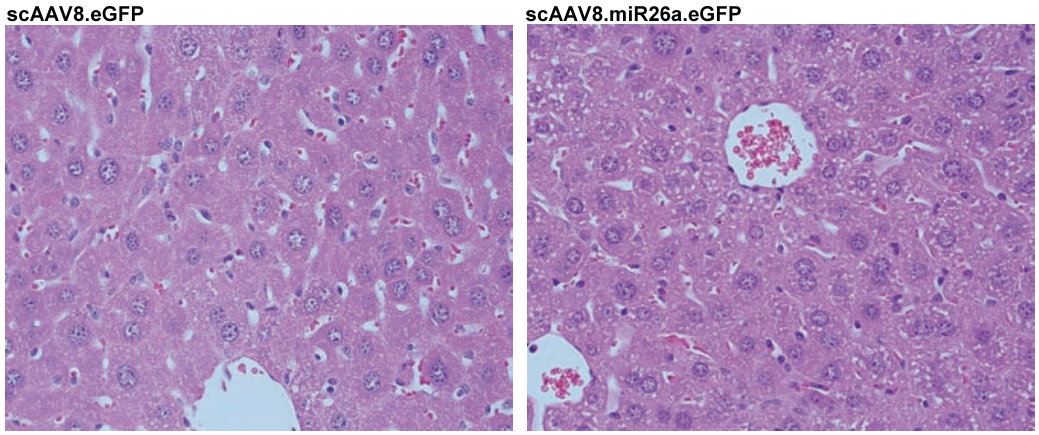
Kota *et al. Cell,* 2009

AAV-mediated *in vivo* miRNA delivery



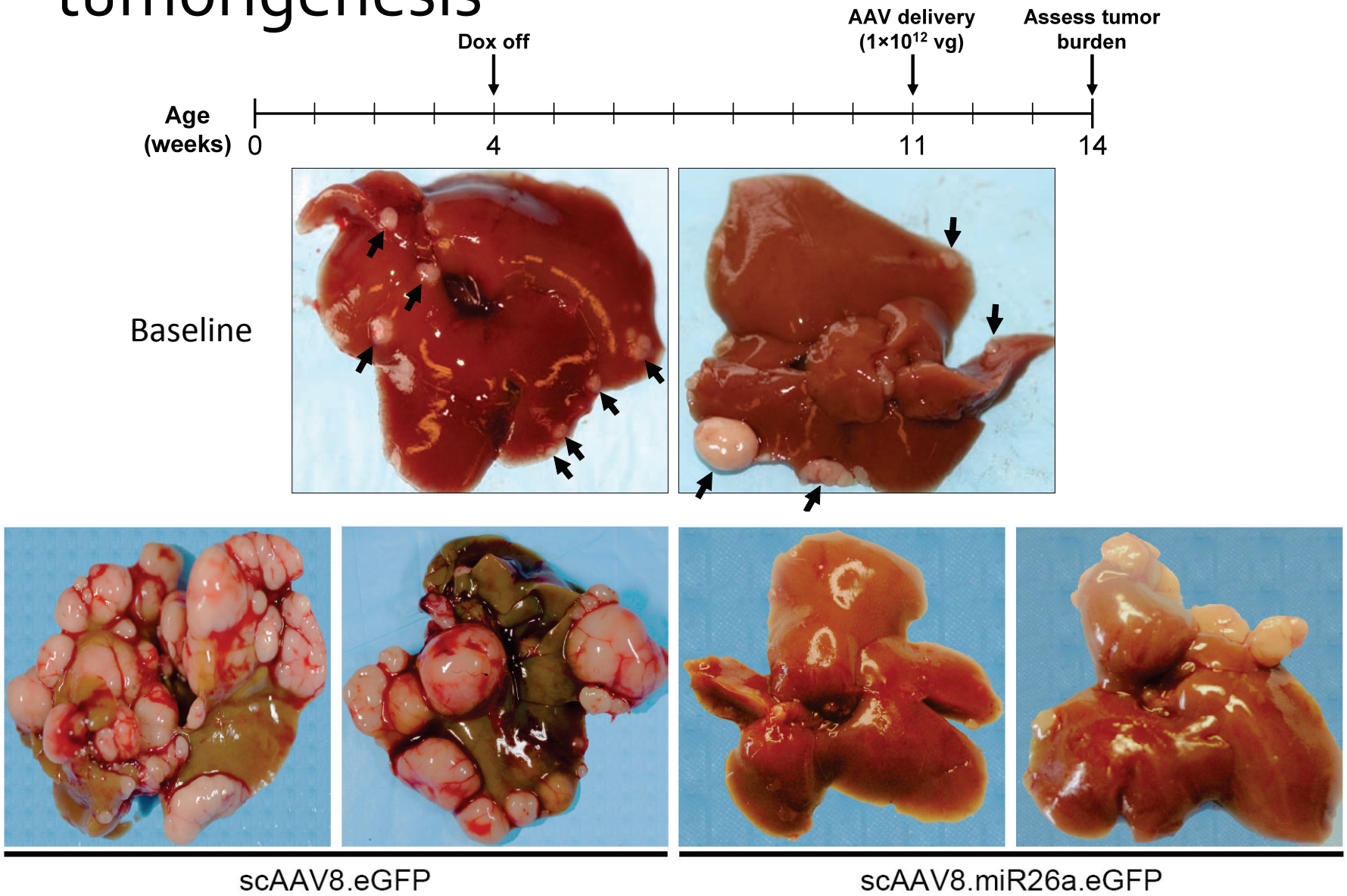






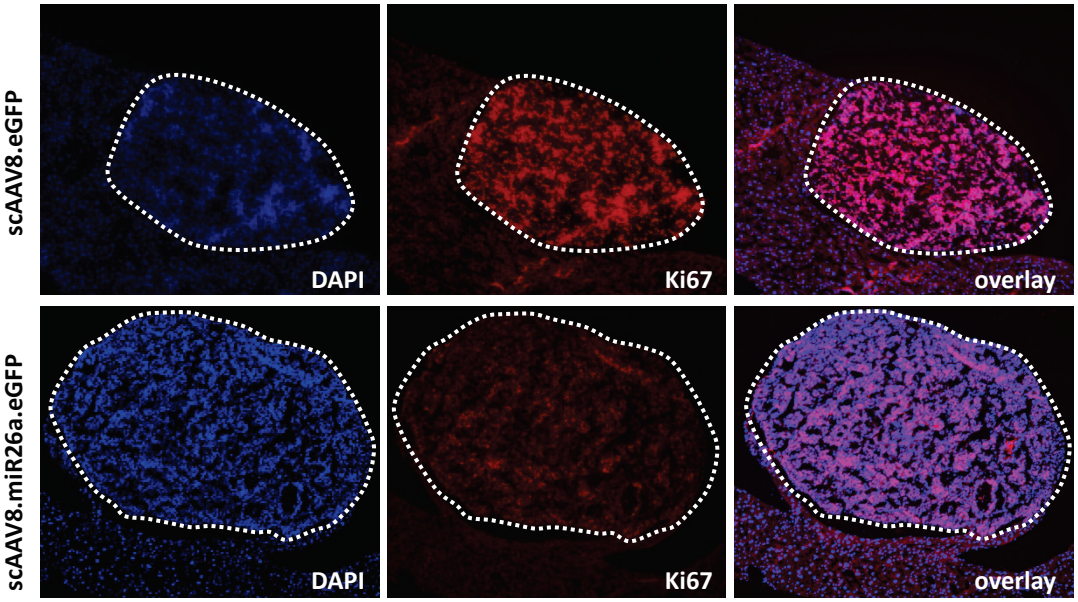
Kota *et al. Cell,* 2009

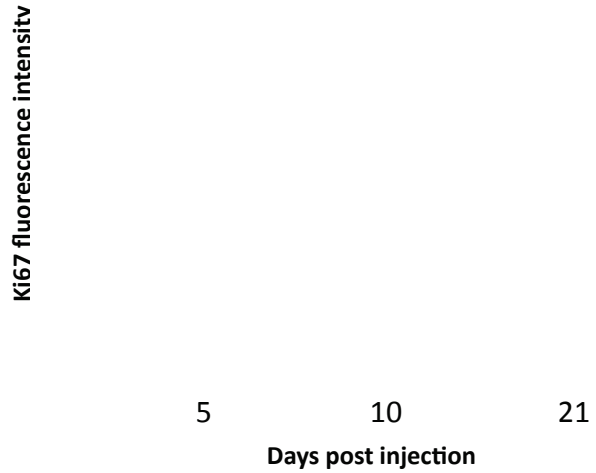
Therapeutic miR-26a delivery suppresses tumorigenesis



Kota *et al. Cell,* 2009

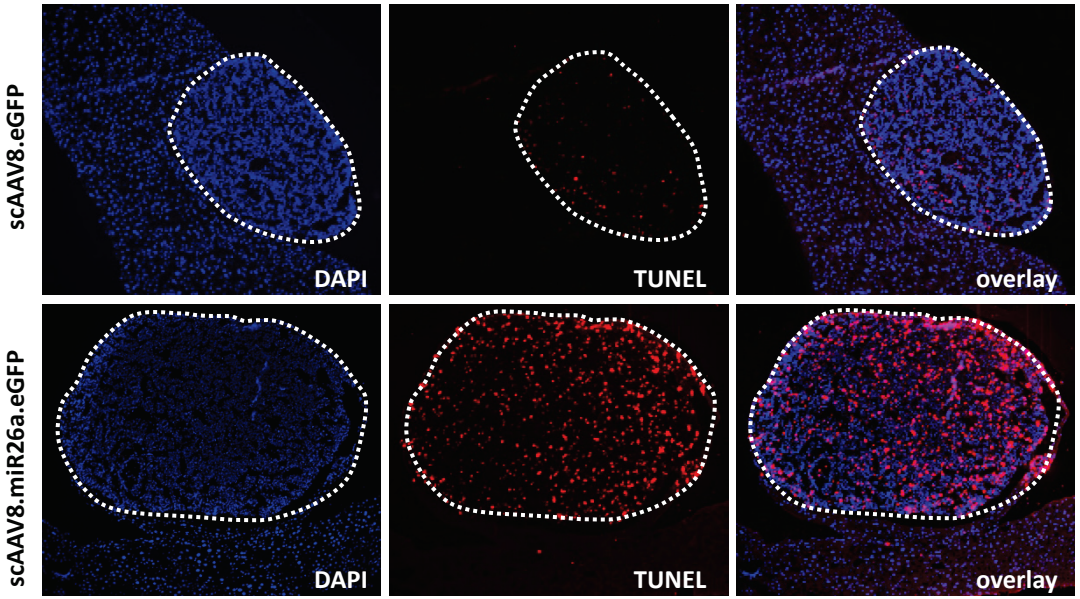
Therapeutic miR-26a delivery arrests proliferation of tumor cells

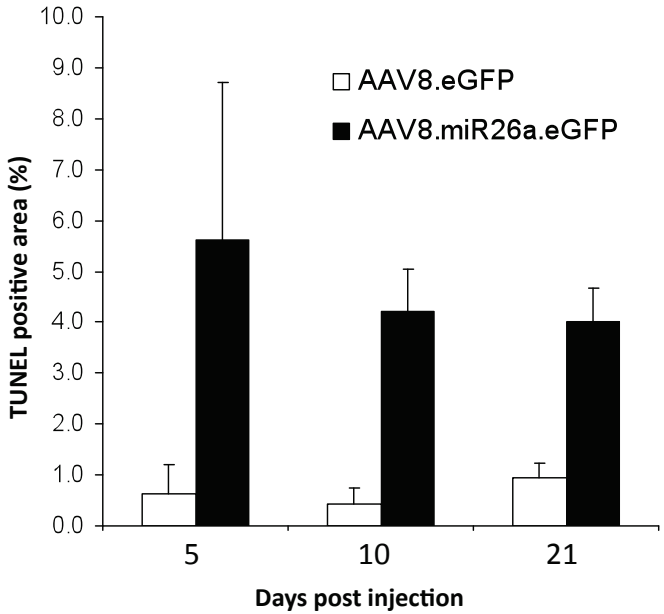




Kota *et al. Cell,* 2009

Therapeutic miR-26a delivery induces tumor-specific apoptosis





Kota *et al. Cell,* 2009

UT Southwestern Molecular Biology

<u>Mendell Lab</u>

Tsung-Cheng Chang
Ana Doughty
Ryan Golden
Antony Hsieh
Yangjian Liu
Sungyul Lee
Lauren Zeitels
Guanglu Shi

Acknowledgements

Johns Hopkins University

Anirban Maitra and lab
Steve Leach and lab
Chi Dang and lab

University of Pennsylvania

Andrei Thomas-Tikhonenko
Michael Dews
Duonan Yu

Nationwide Children's

Janaiah Kota
Jerry Mendell
Reed Clark

Ohio State University

Kalpana Ghoshal

HHMI HOWARD HUGHES MEDICAL INSTITUTE

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