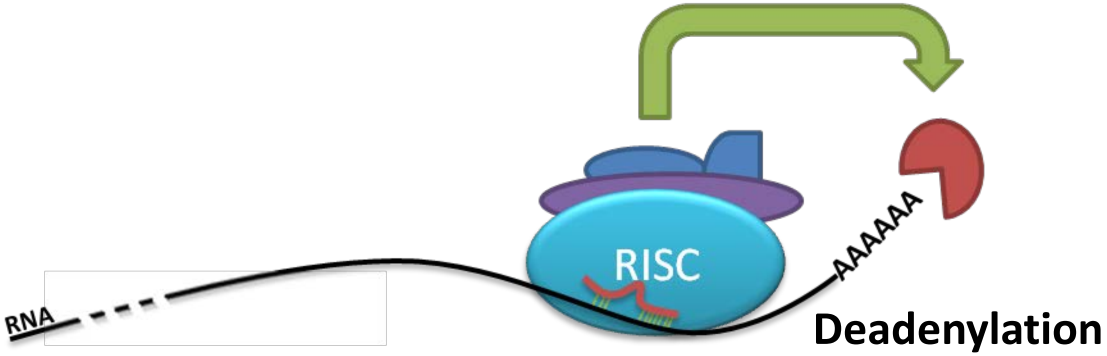
Using TCGA samples to infer Post-Transcriptional Regulation in Cancer

Pavel Sumazin
Califano Lab, Columbia University

Post-transcriptional regulation by microRNAs



microRNAs (**miR**s) post-transcriptionally regulate RNAs through multiple mechanisms including transcript degradation and translational repression

miRs can act as tumor suppressors and as oncomiRs

Integrating transcriptional and post-transcriptional regulation by miRs

To understand how miRs and genes interact:

1. Transcriptional regulation of miRs
2. Post-transcriptional regulation of miRs
3. Regulation by miRs
4. Regulation of miR activity

TCGA large scale same-sample profiles of mRNA and miR expression provide the data needed for computational prediction

Integrating transcriptional and post-transcriptional regulation

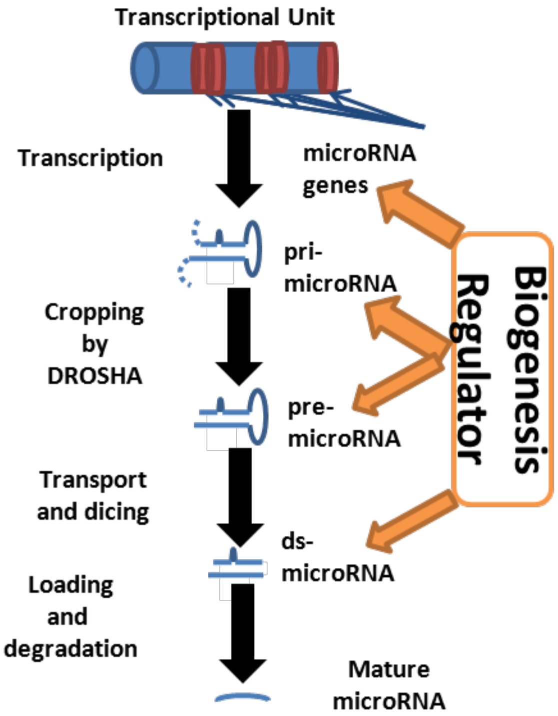
To understand how miRs and genes interact:

(1) Transcriptional regulation of miRs
(2) Post-transcriptional regulation of miRs
(3) Regulation by miRs
(4) Regulation of miR activity

TCGA large scale same-sample profiles of mRNA and miR expression provide the data needed for computational prediction

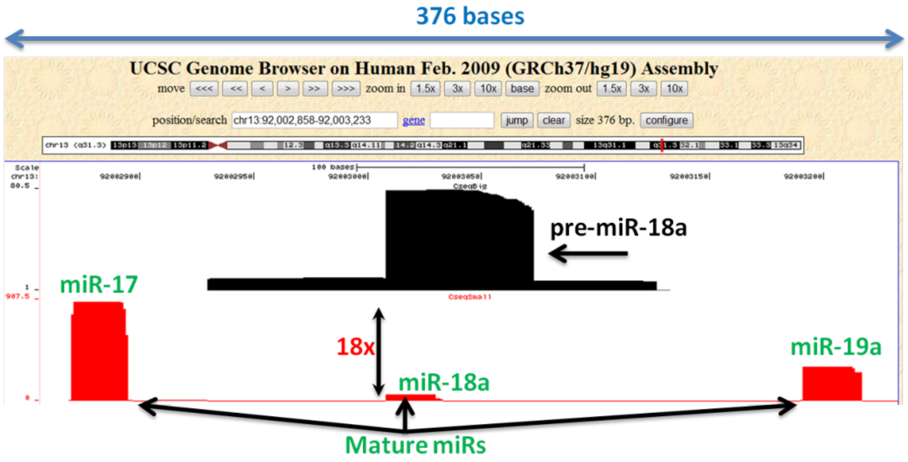
Post-transcriptional regulation of miRs

Tight post-transcriptional control leads to significant swings in mature miR expression



Post-transcriptional regulation of miRs

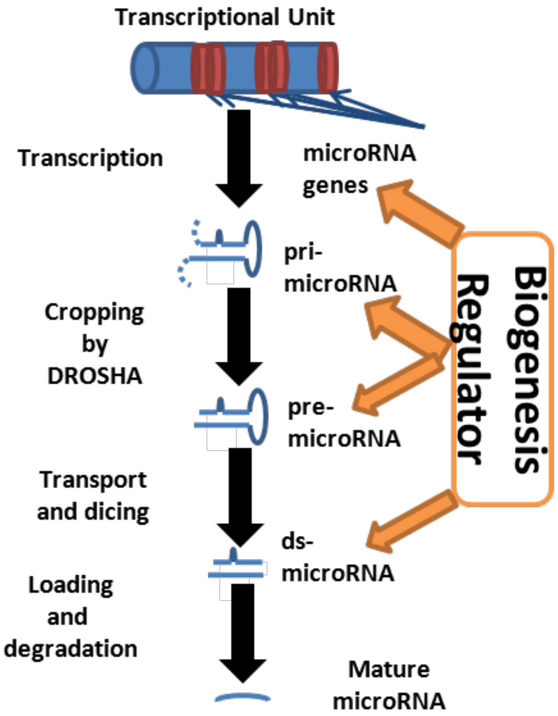
Tight post-transcriptional control leads to significant swings in mature miR expression



UCSC Genome Browser on Human Feb. 2009 (GRCh37/hg19) Assembly

position/search chr13:92,002,858-92,003,233 gene size 376 bp.

SNB19 (GBM cell line)



Transcriptional Unit

Transcription

microRNA genes

pri-microRNA

Cropping by DROSHA

pre-microRNA

Transport and dicing

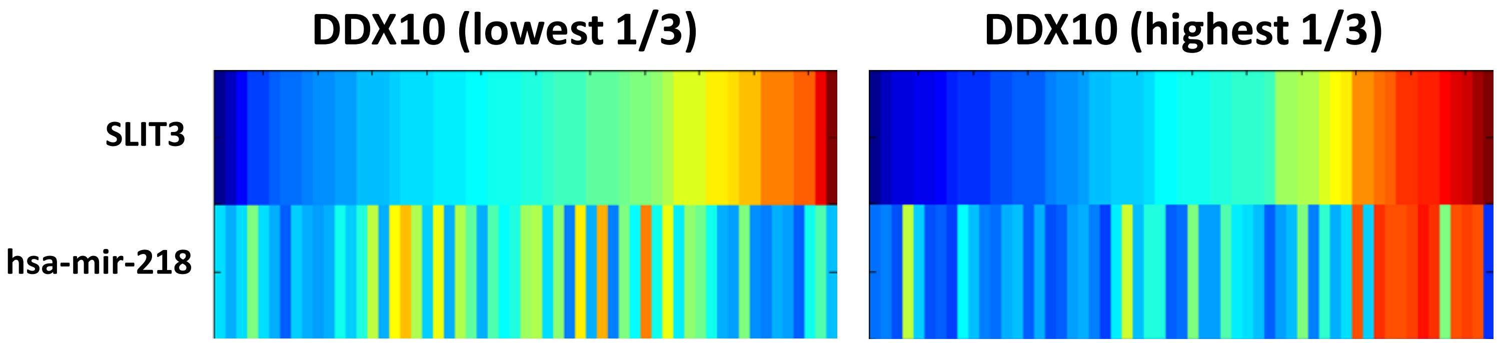
ds-microRNA

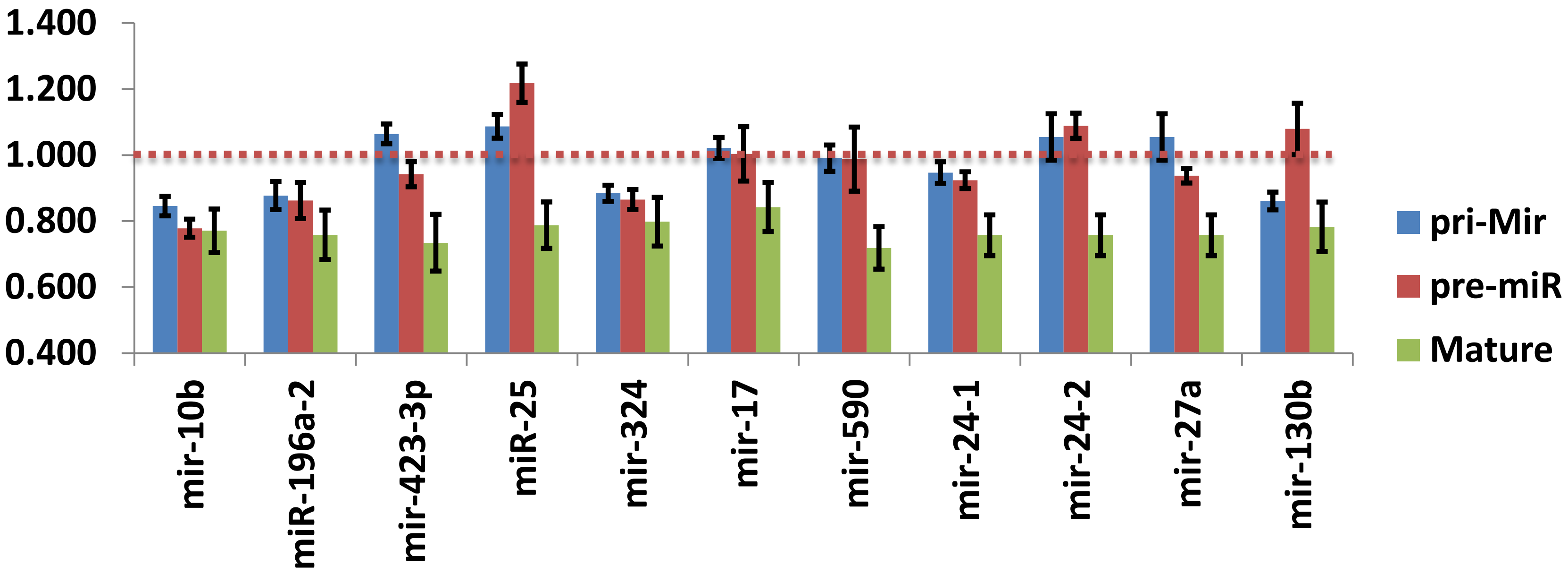
Loading and degradation

Mature microRNA

Biogenesis Regulator

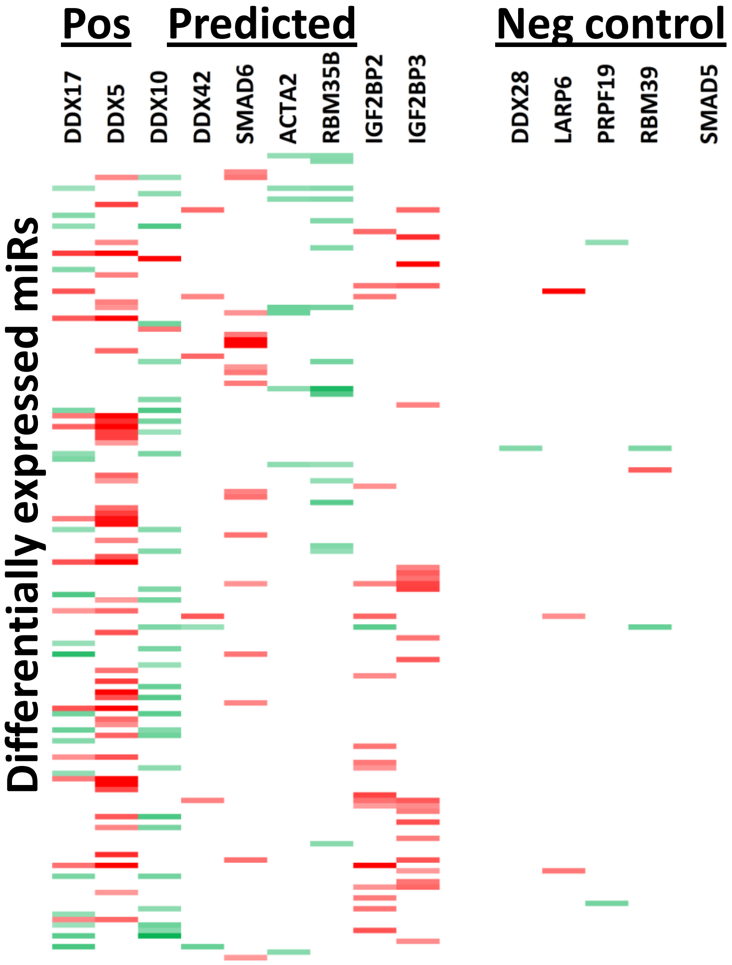
DDX10 up regulates miR biogenesis in SNB19





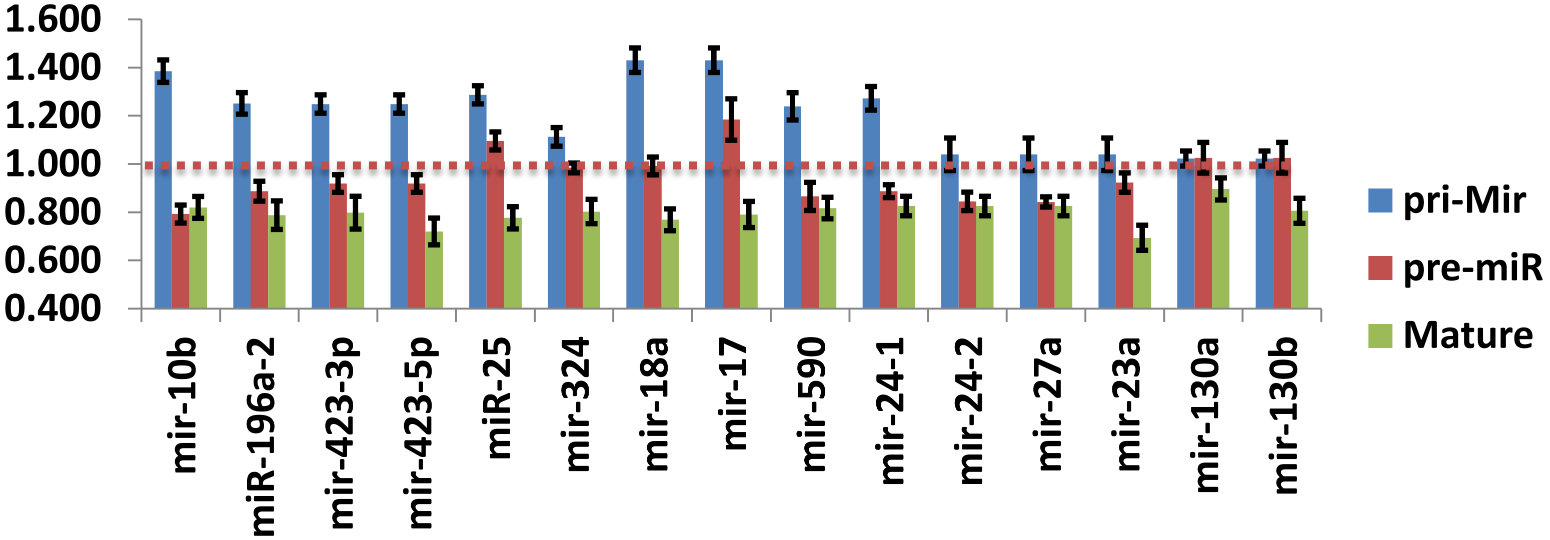
miR biogenesis regulators in SNB19

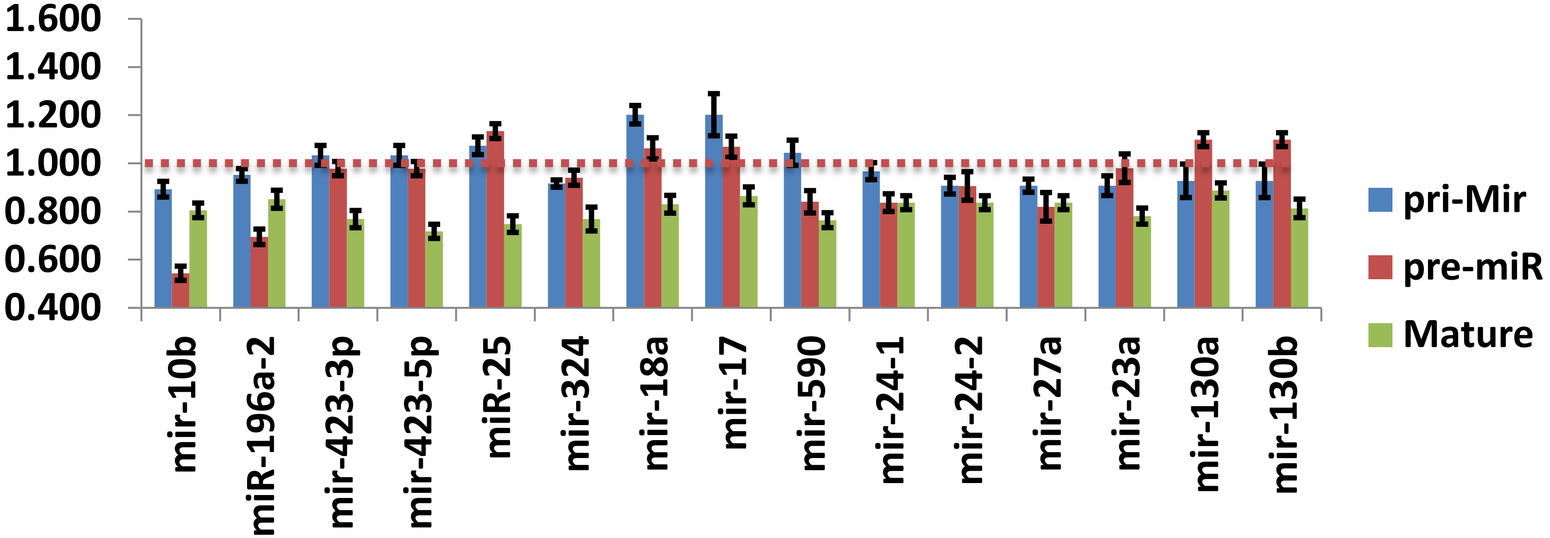
miRNome-wide profiling in response to regulator silencing, including positive and negative controls, suggests miR specific regulation



Enriched DDX10 binding motif

miR biogenesis regulators in SNB19





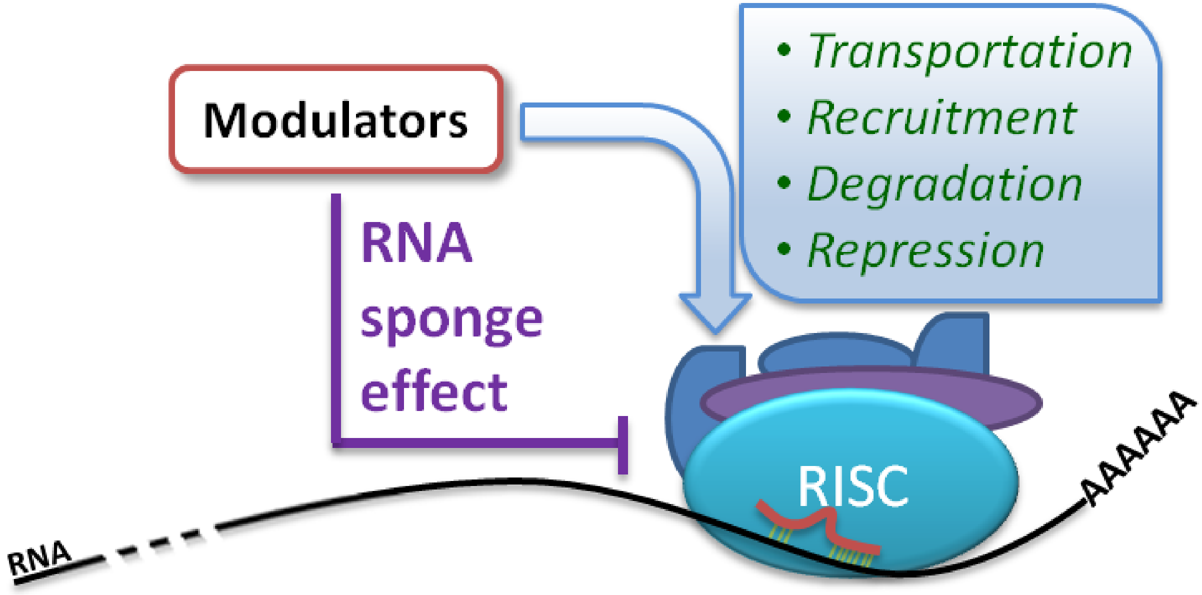
Integrating transcriptional and post-transcriptional regulation

To understand how miRs and genes interact:

(1) Transcriptional regulation of miRs
(2) Post-transcriptional regulation of miRs
(3) Regulation by miRs
(4) Regulation of miR activity

TCGA large scale same-sample profiles of mRNA and miR expression provide the data needed for computational prediction

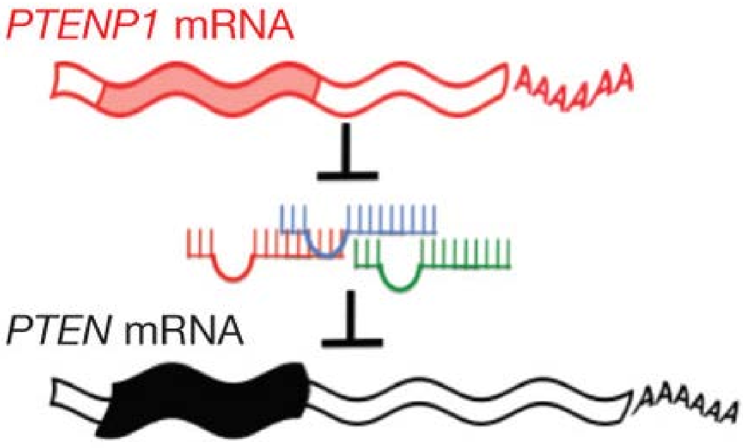
Regulation of miR activity



We distinguish between two types of regulators (modulators):

1. *Sponge regulators* compete for miR programs that regulate other RNAs
2. *Non-sponge regulators* activate or suppress miRISC-mediated regulation of target RNAs

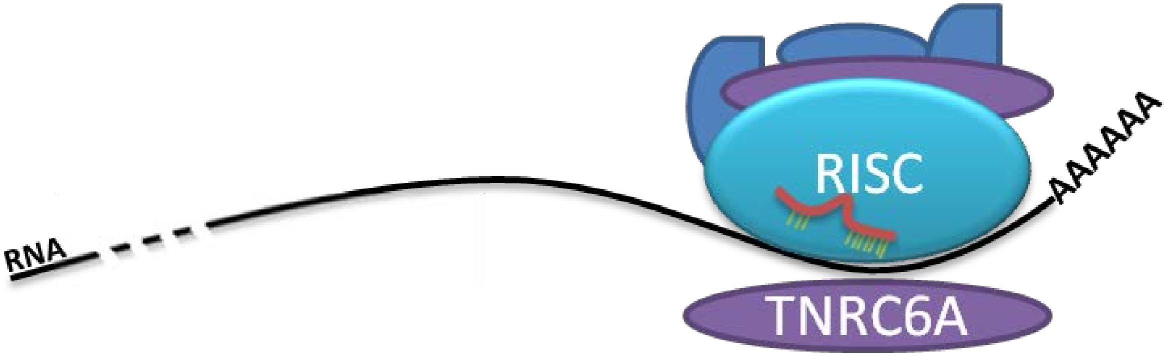
Sponge regulators



Poliseno & Salmena et al., 2010

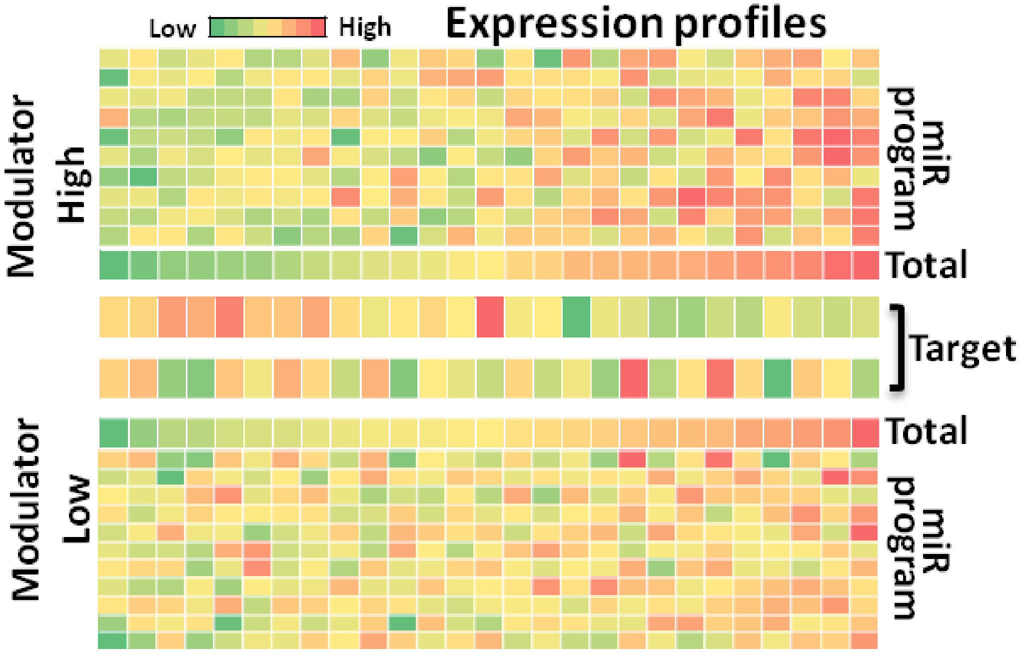
PTEN is a tumor suppressor and a key regulator of cancer
PTEN and PTENP1 have common miR regulators
Changes to PTENP1 expression modify the post-transcriptional regulatory program that targets PTEN

Non-Sponge regulators



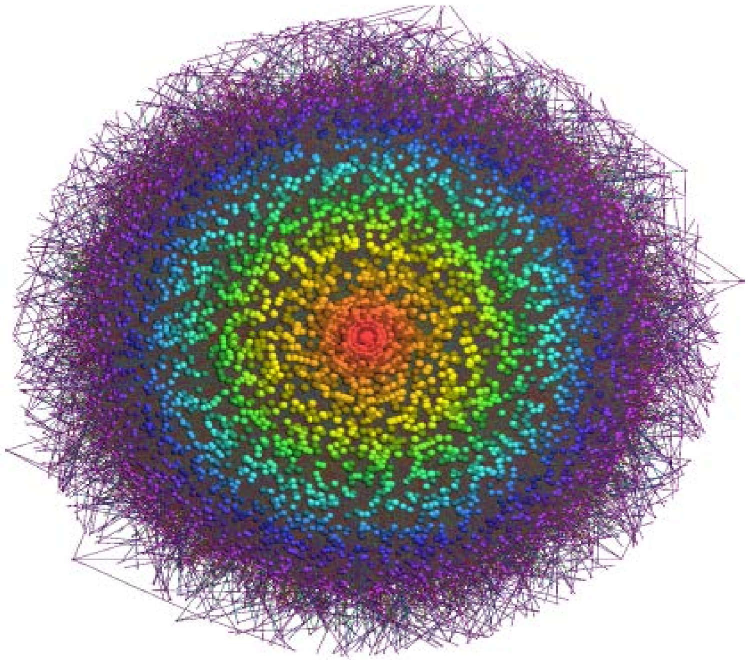
TNRC6 (GW182) proteins are required for miRISC function
Deleterious somatic mutations to TNRC6A may contribute to tumorigenesis of gastric and colorectal cancers (Kim et al., 2010)

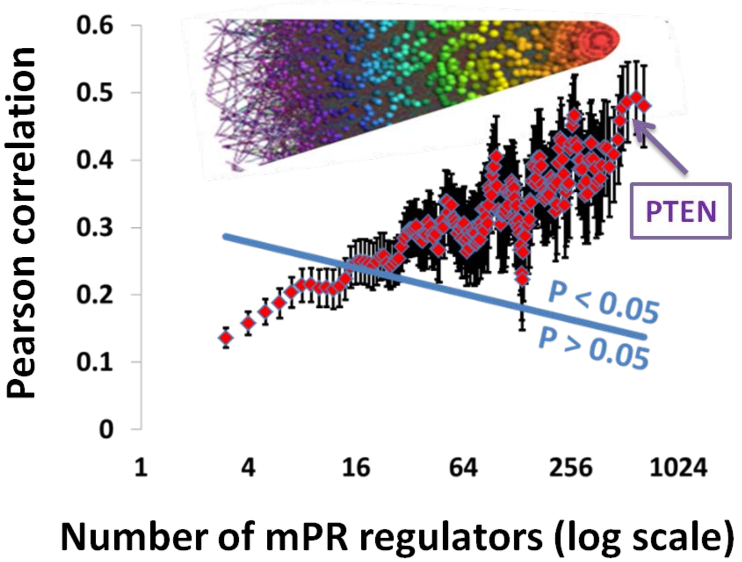
Genome-wide screening for modulators



Conditional regulation through a miR program:
Stronger inverse correlation between the miR program and its target is evident when modulator expression is high

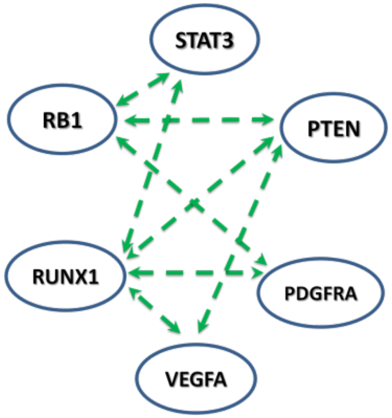
miR-Program mediated Regulatory (mPR) network



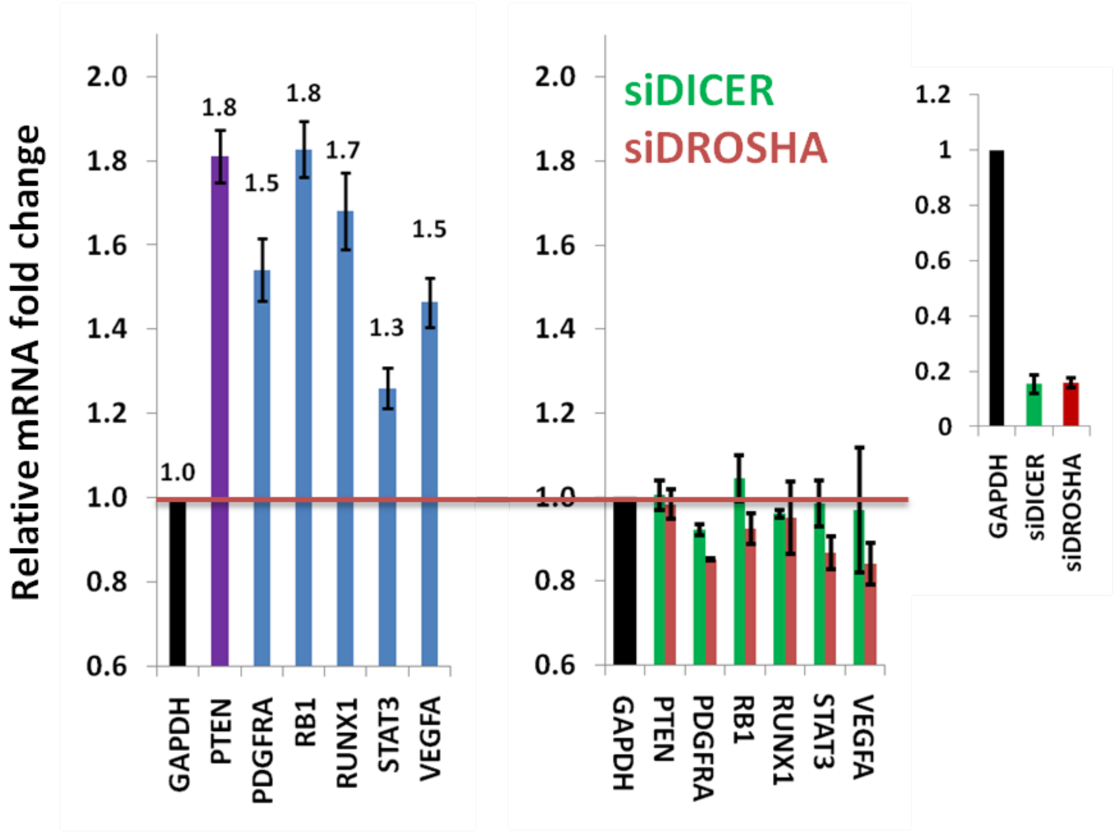


TCGA GBM mPR network: ~7,000 genes in ~248,000 interactions

Established drivers of gliomagenesis form a tightly regulated mPR subnetwork

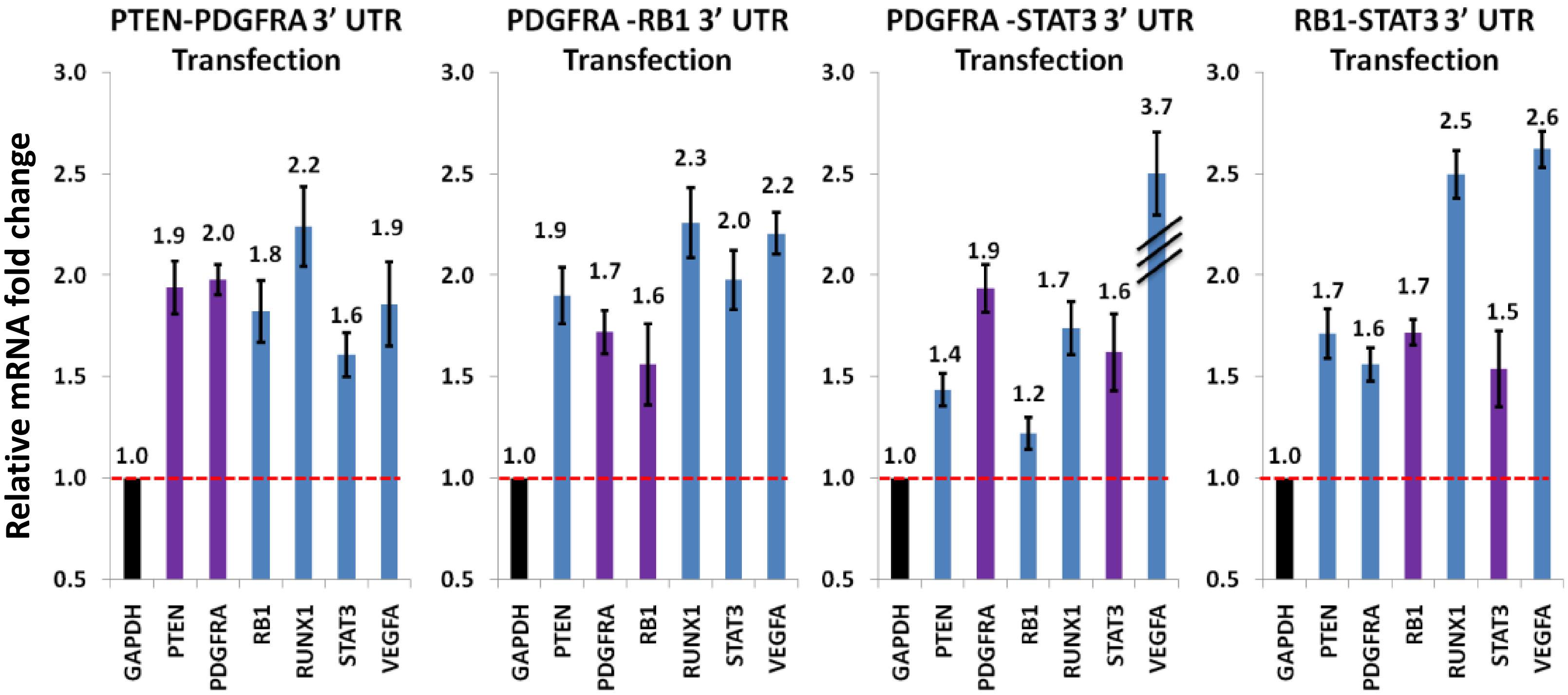


Transfection with PTEN 3’ UTR upregulated other GBM drivers in a DICER- DROSHA-dependent manner:



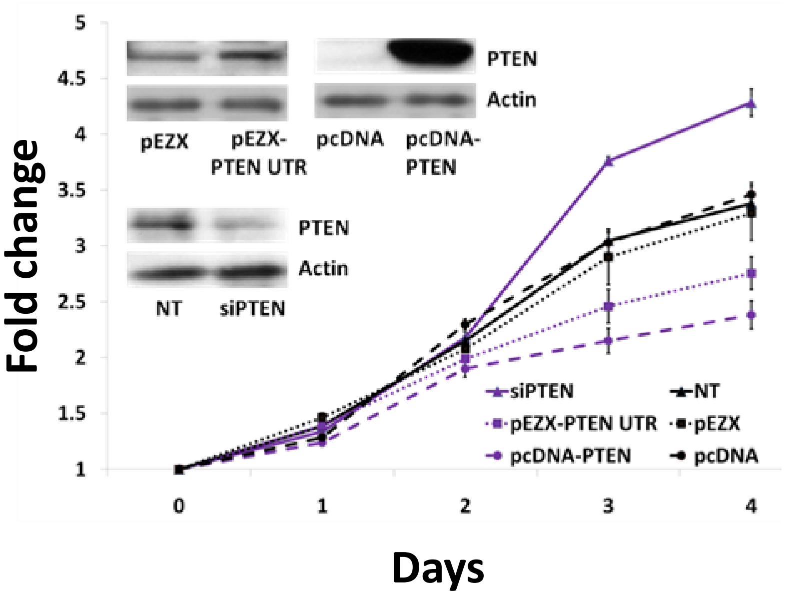
Established drivers of gliomagenesis form a tightly regulated mPR subnetwork

Transfections with 3’ UTR pairs, at 50% each:

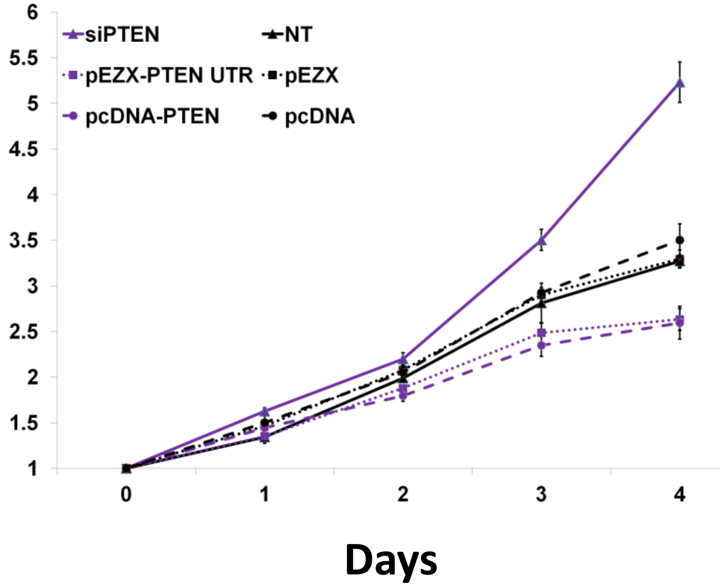


PTEN regulates tumor cell growth rates

SNB19 cell growth rate

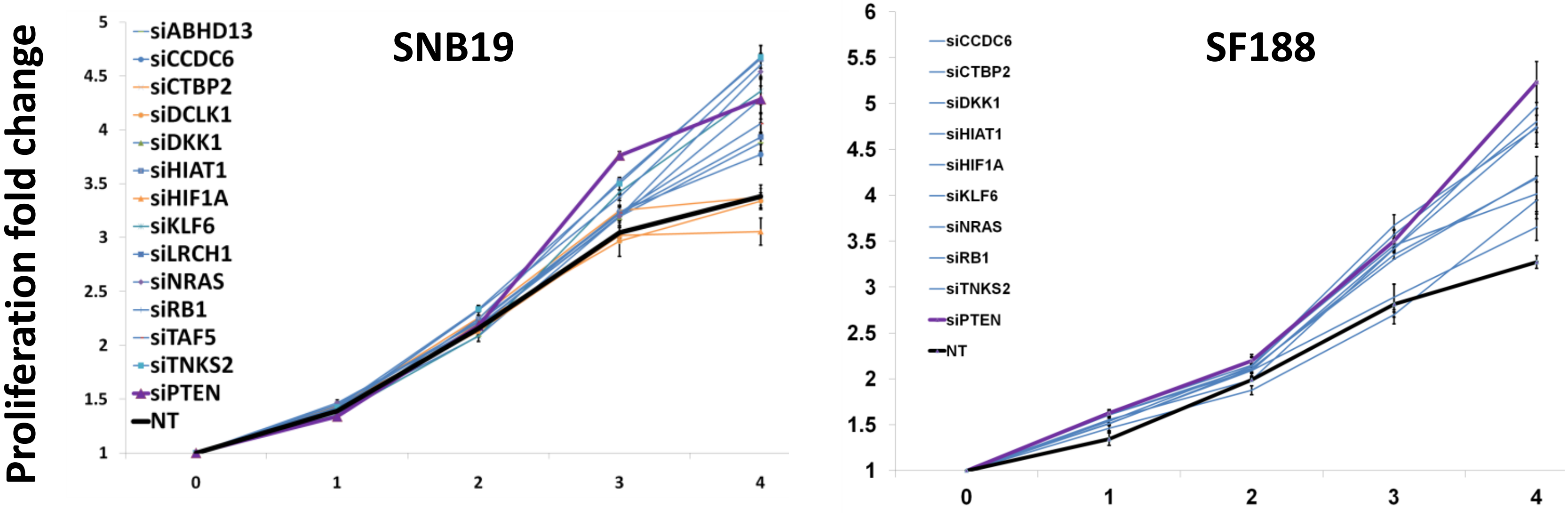


SF188 cell growth rate



Changes to PTEN expression correlate with Glioblastoma cell growth rates

mPR regulators affect tumor cell growth rates



Silencing PTEN mPR regulator whose loci is deleted in samples where PTEN is intact accelerates tumor cell growth

Acknowledgements

Computational:

Hua-Sheng Chiu

Wei-Jen Chung

Mukesh Bansal

Paolo Guarnieri

Labs:
Andrea Califano
Jose Silva

Experimental:
Xuerui Yang
David Llobet-Navas
Archana Iyer
Presha Rajbhandari

Thank you for listening! Questions?