

Current microRNA target identification methods are heavily contaminated with false positives

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November 8, 2018

This slideshow is available at:

<http://www.igh.cnrs.fr/equip/Seitz/Sifr2018.pdf>

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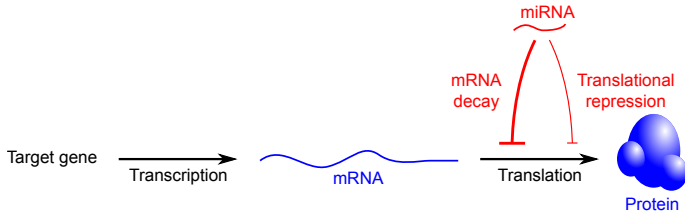
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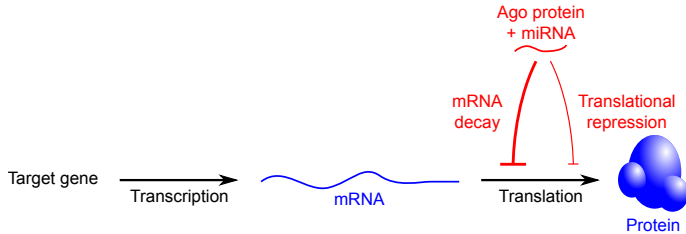
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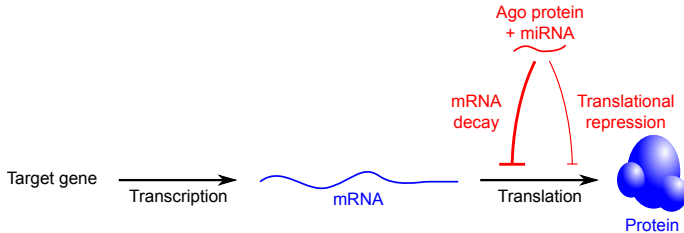
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miRNA sequences are known (for the most part); can we identify their targets ?

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- ▶ Sequence complementarity to the miRNA.
- ▶ Physically bind the miRNA effector complex.
- ▶ mRNA and protein level respond to miRNA.

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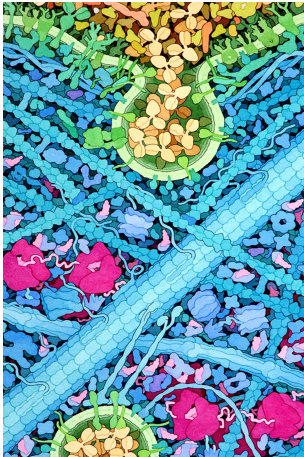
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(illustration by D. Goodsell, Scripps Research Institute and Rutgers University)

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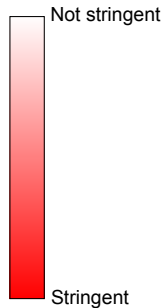
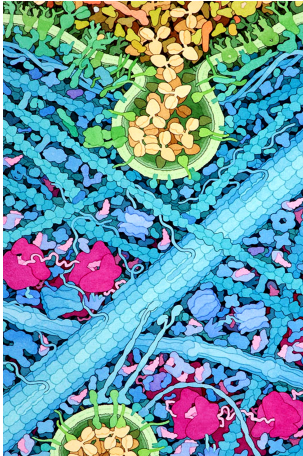
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Comparative genomics dogma:
if it is conserved, it must be functional.

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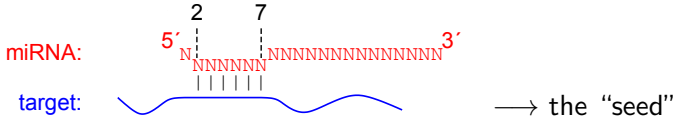
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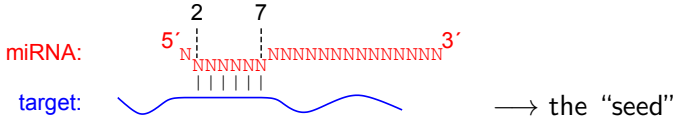
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Comparative genomics (if a seed match is conserved, it must be functional).

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- ▶ Experimental methods (CLIP and avatars): hundreds of targets per miRNA.
- ▶ Computational methods (seed matches, conserved in evolution): hundreds of targets per miRNA.

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miRNA-mediated repression is very modest (usually < 2 -fold): lower than well tolerated fluctuations in gene expression (e.g., haplosufficiency).

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miRNA-mediated repression is very modest (usually < 2 -fold): lower than well tolerated fluctuations in gene expression (e.g., haplosufficiency). Why have these sites been conserved if they are not functional?

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Baek *et al.*, 2008: quantification of miR-223-mediated repression in mouse neutrophils.

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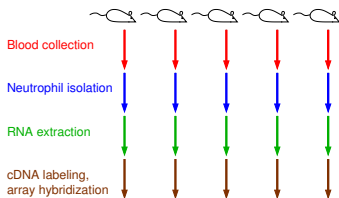
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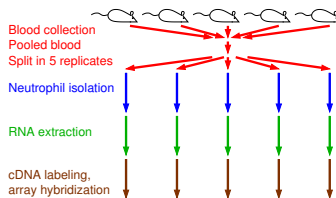
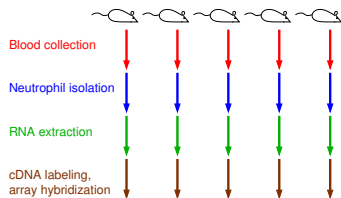
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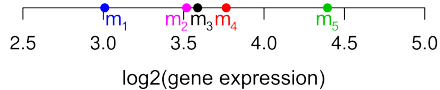
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Gene *Styx*



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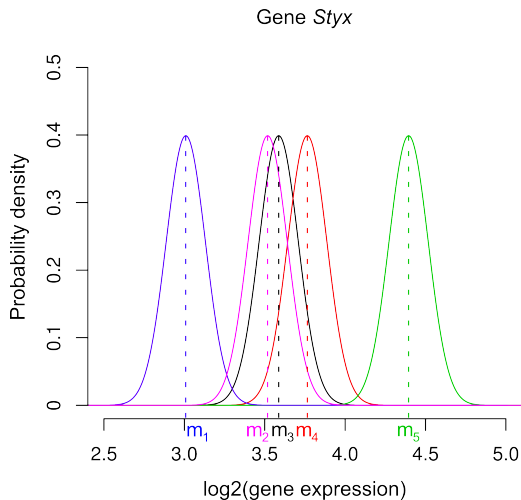
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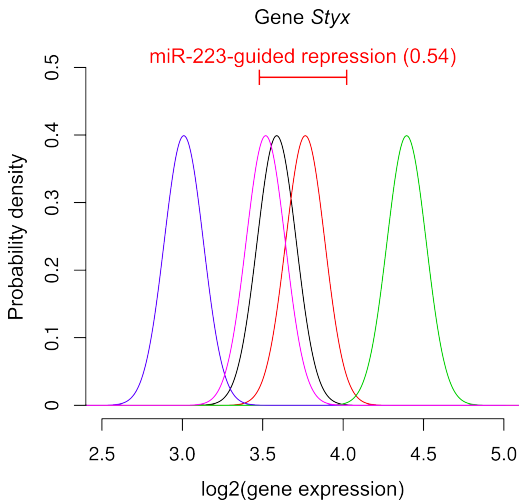
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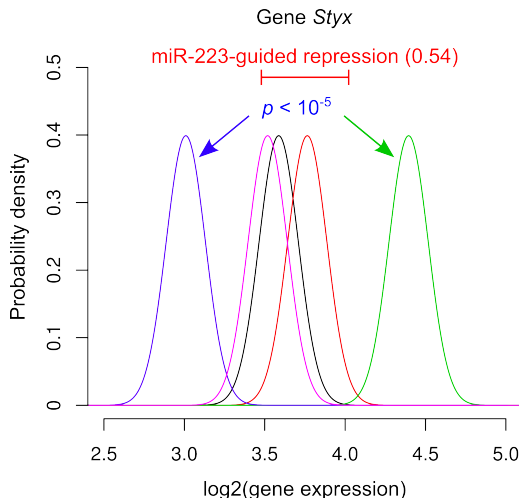
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p : probability that the difference between two individual mice is smaller than miRNA-guided repression

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For 150 predicted targets out of 192:
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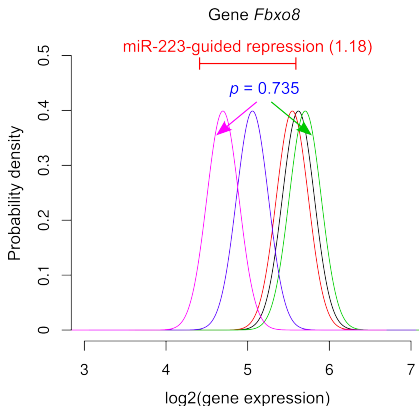
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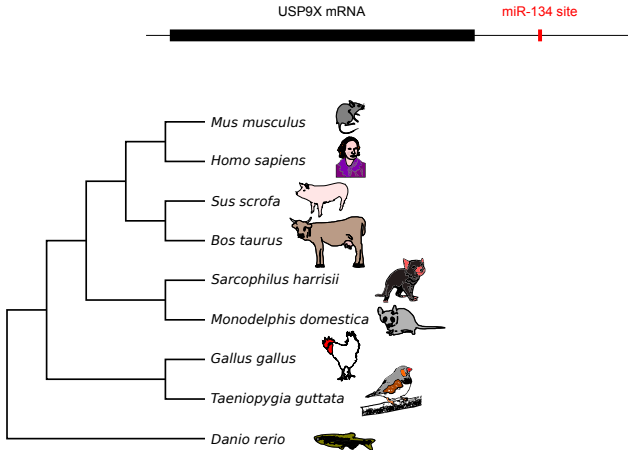
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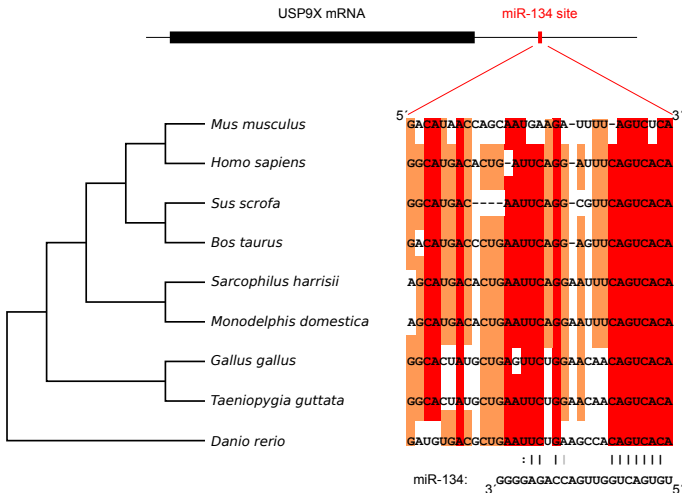
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■ : conserved in 8 or 9 species out of 9 ■ : conserved in 6 or 7 species out of 9 □ : conserved in less than 6 species out of 9

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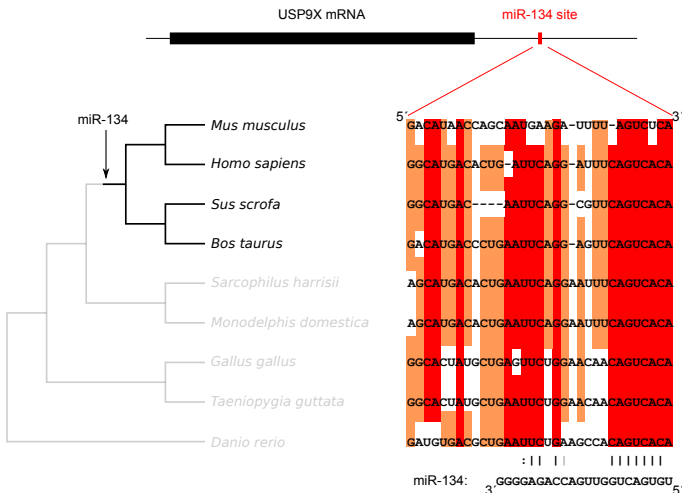
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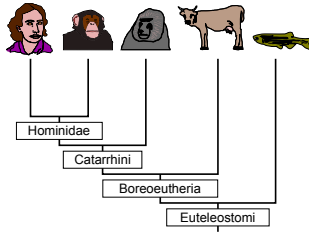
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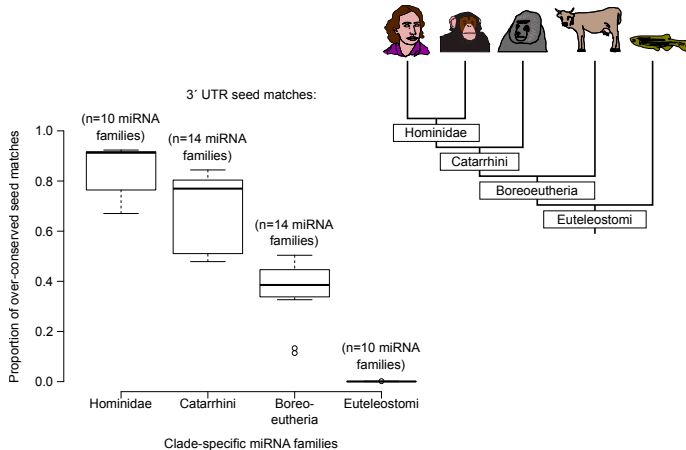
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► Comparison to prediction programs

► Effect of tree architecture

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Most known miRNA “targets” are probably not *functionally* targeted.

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Observing a molecular event does not mean that it has a biological function.

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Most known miRNA “targets” are probably not *functionally* targeted.

Observing a molecular **object** does not mean that it has a biological function.

Homeostasis attenuates changes of external origin: it also buffers internal changes.

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Collaborators: F. Apparailly, J. Presumey (INM, Montpellier)



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October 2019: CNRS « école thématique » on small regulatory RNAs (miRNAs, siRNAs, piRNAs) in Sète.

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▸ CLIP and avatars

▸ Overconservation statistics

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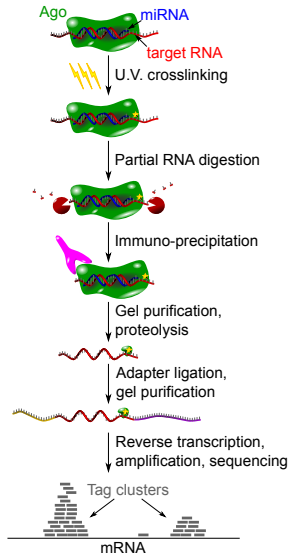
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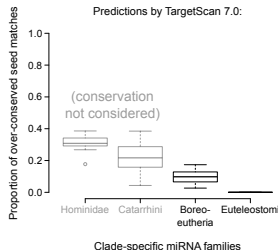
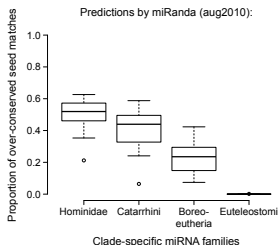
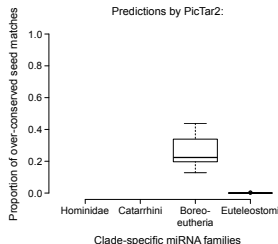
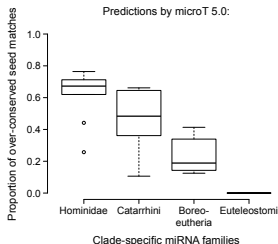
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