Assessment of miRNA-controlled phenotypes from a functional perspective: the example of miR-34-guided control of cell proliferation

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This slideshow is available at:
`http://www.igh.cnrs.fr/equip/Seitz/GSO2018.pdf`

Introduction

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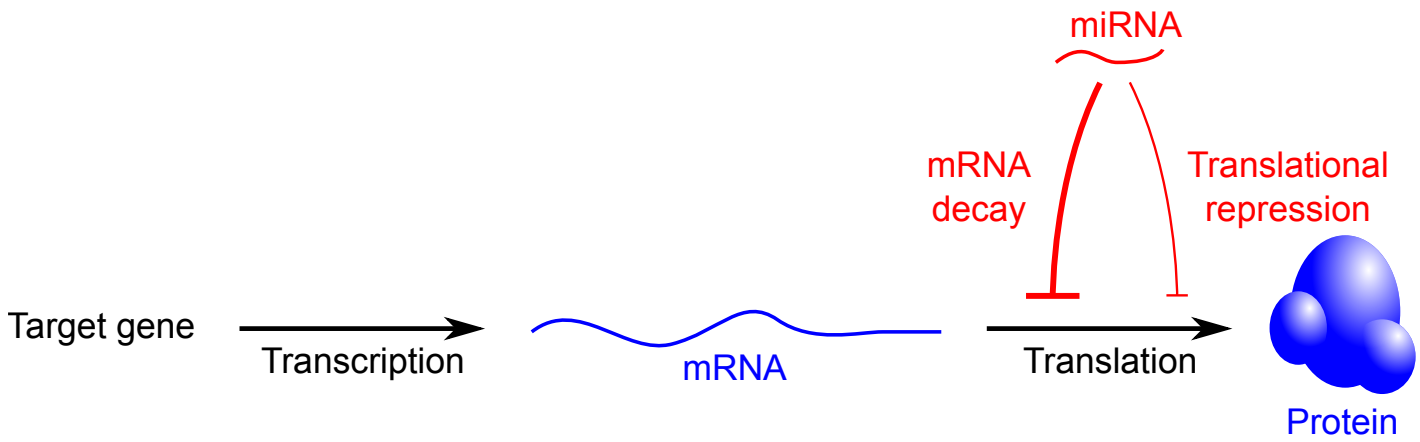

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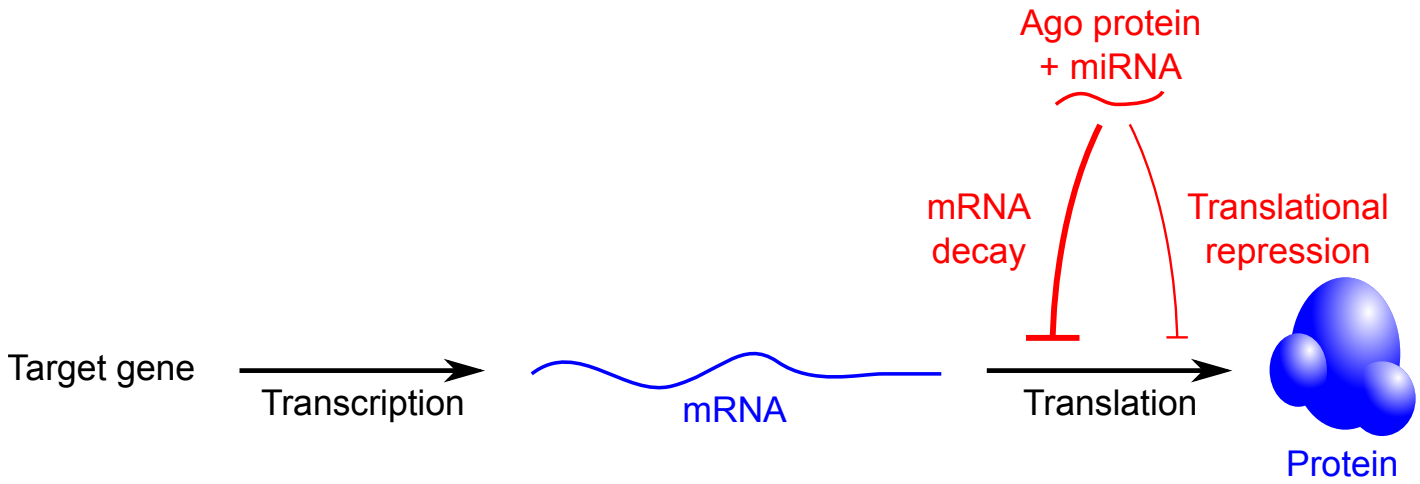

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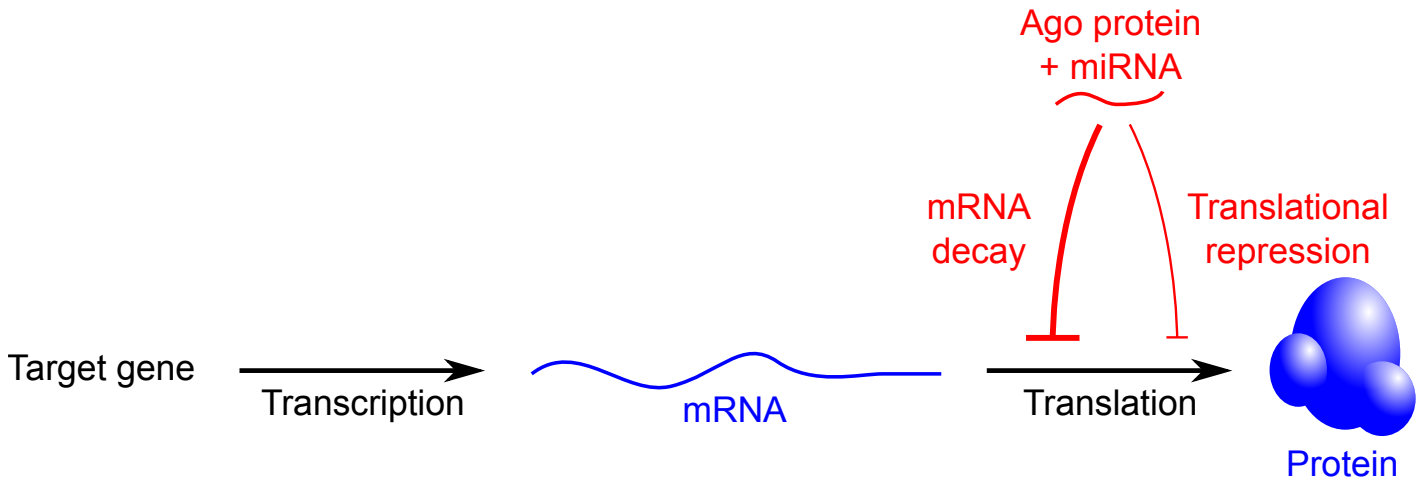

miRNA sequences are known (for the most part); can we identify their targets ?

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- Physically bind the miRNA effector complex.
- mRNA and protein level respond to miRNA (cannot distinguish direct from indirect targets).

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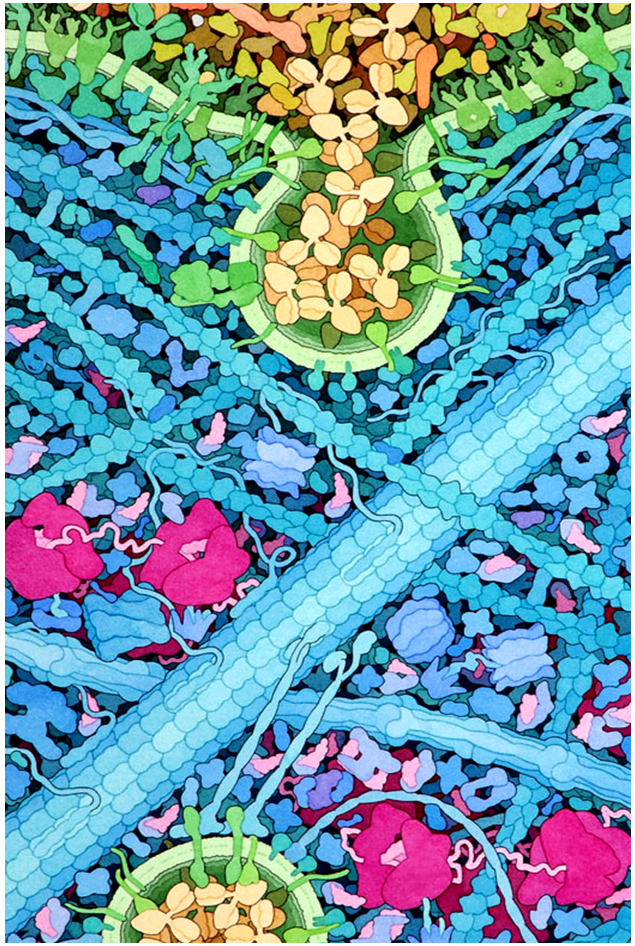

(illustration by D. Goodsell, Scripps Research Institute and Rutgers University)

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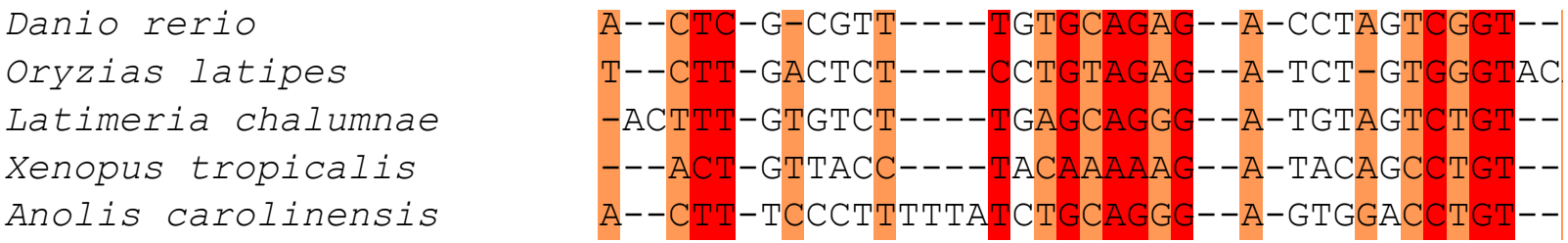

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Comparative genomics dogma:
if it is conserved, it must be functional.

Computational prediction programs are useful, even if you identified miRNA targets by an experimental method (CLIP, differential transcriptomics, ...).

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Relevance in cancer research: miR-34 represses cell proliferation (He *et al.*, 2007), but the mechanism is unknown. The only cancer-related miRNA clinical trial (miR-34 mimick "MRX34") is a failure.

▸ CLIP and avatars

Results

Comparative genomics yield false positives

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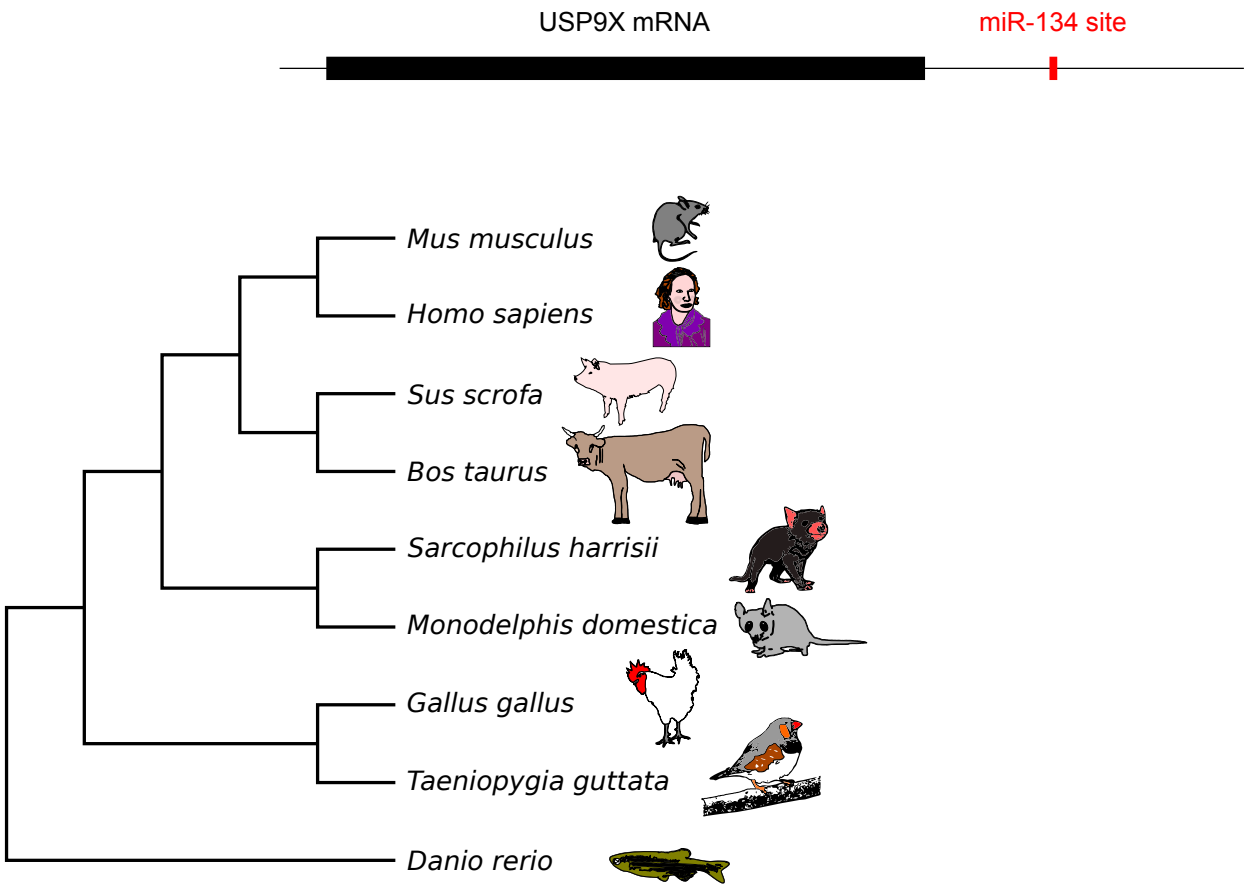

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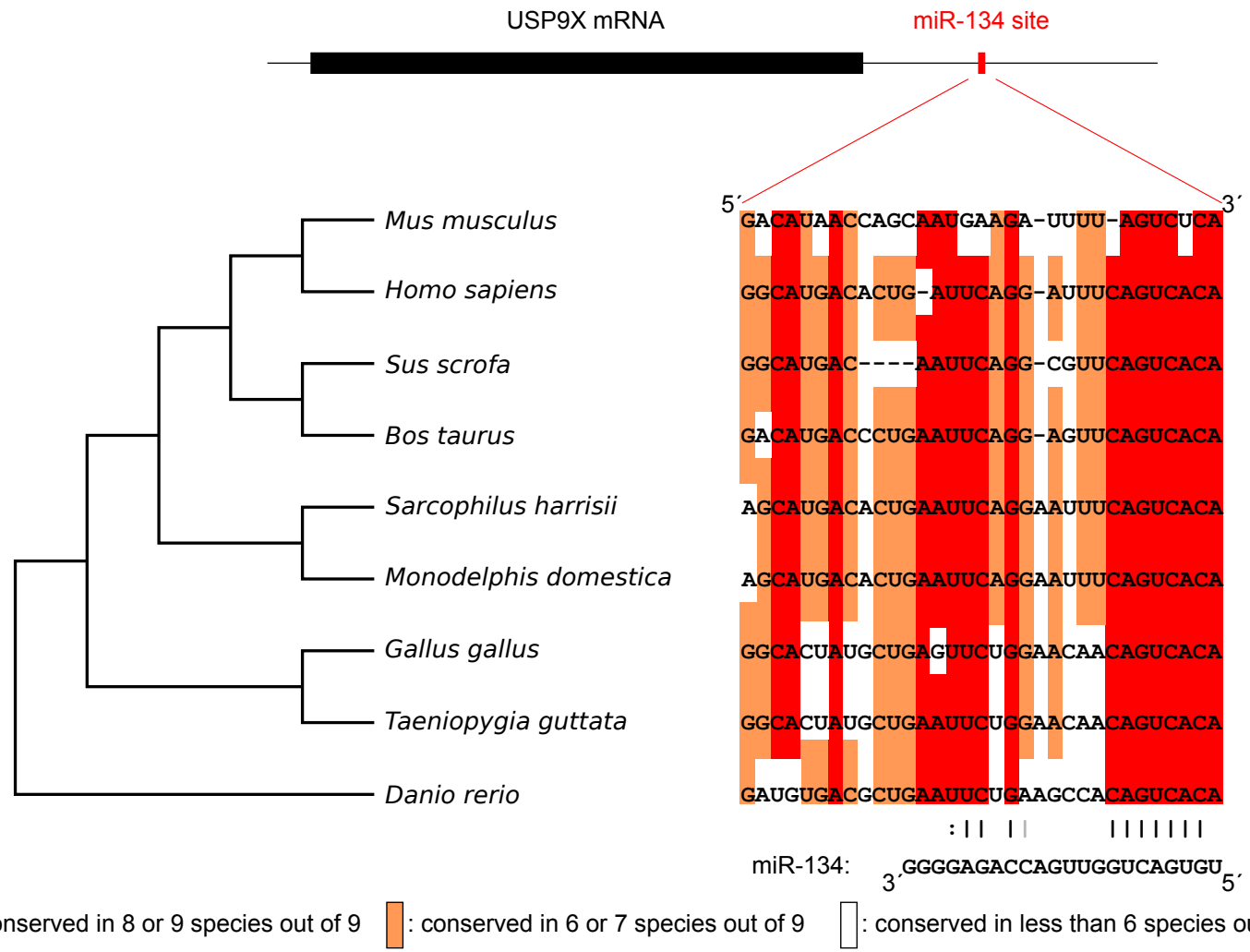

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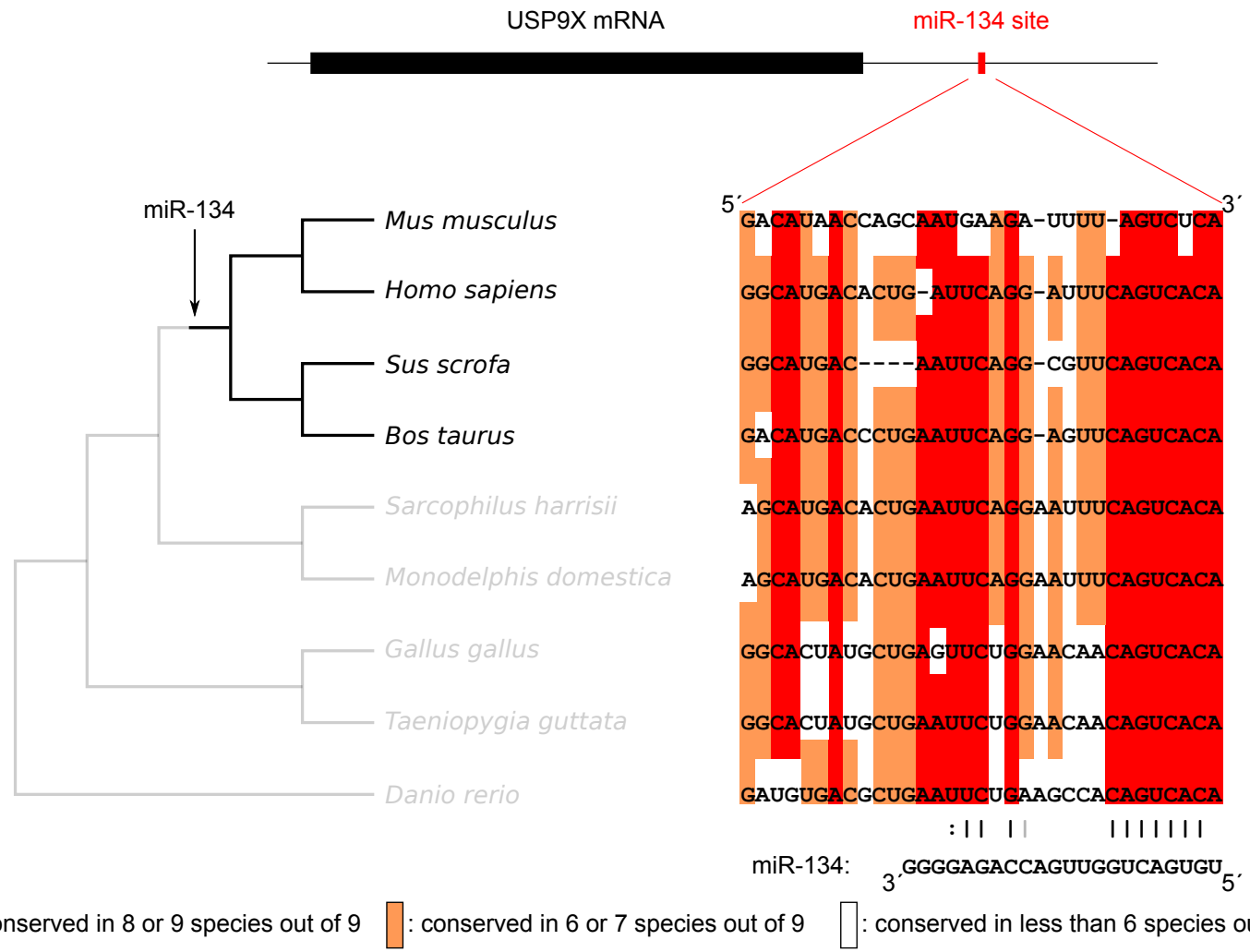

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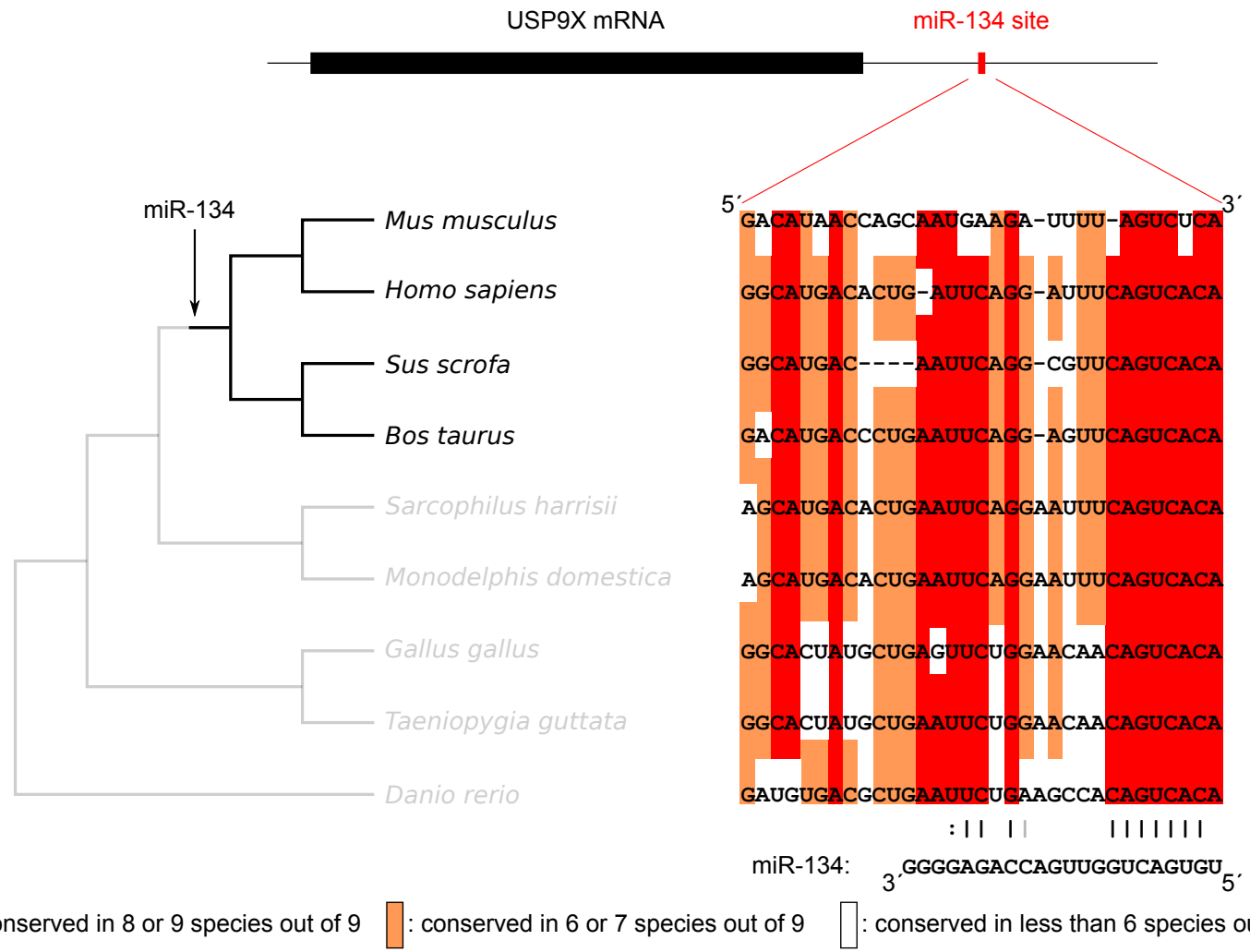
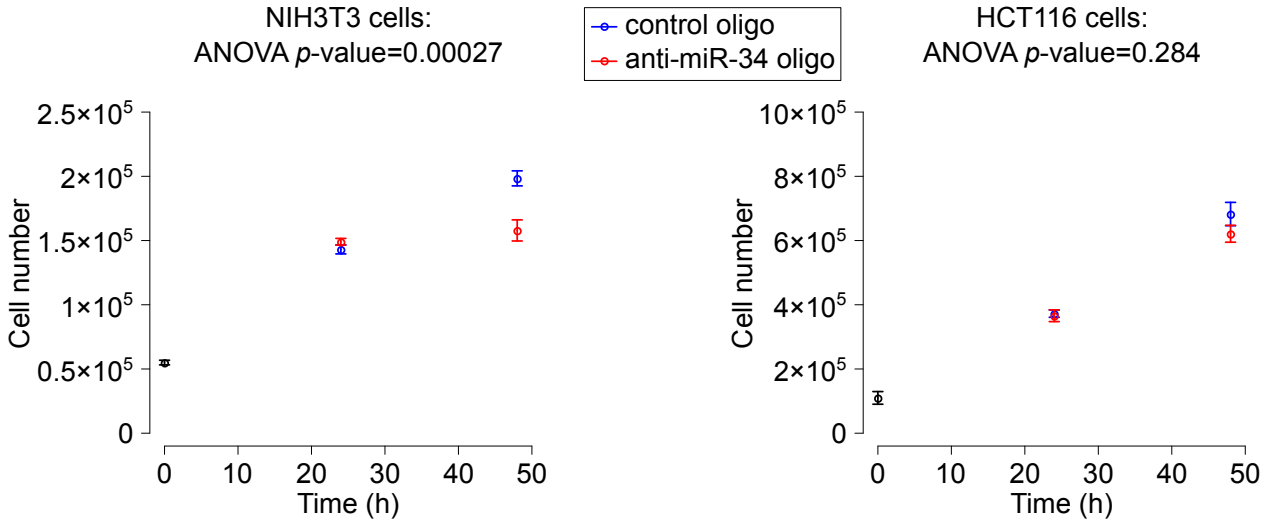


▸ Quantifying overconservation

miR-34 and proliferation

He *et al.*, 2007: over-expression of miR-34 represses cell proliferation in various human and murine cell lines.

miR-34 and proliferation



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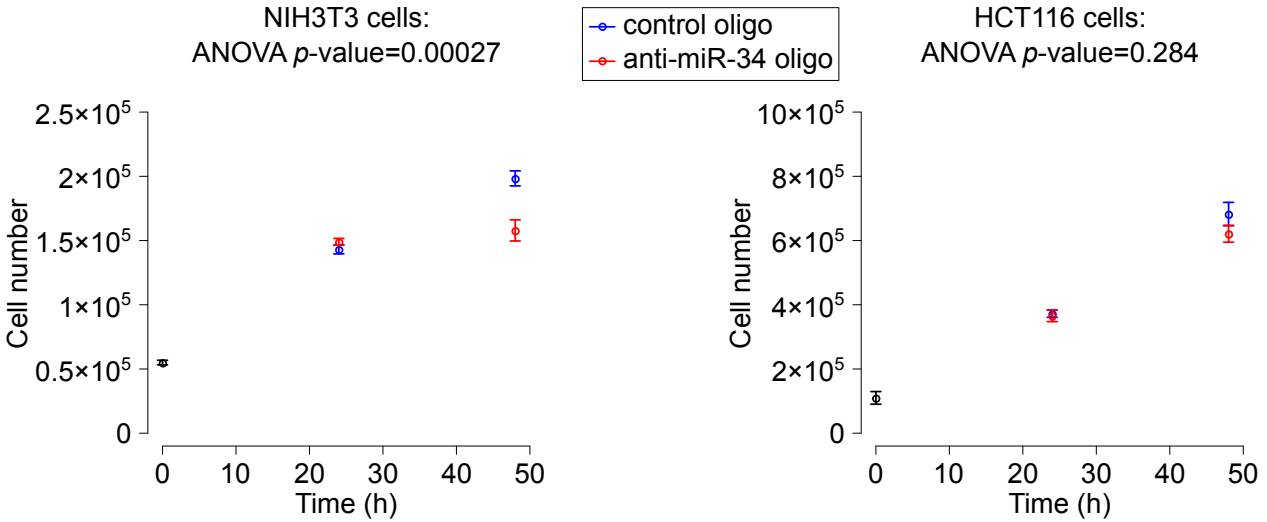

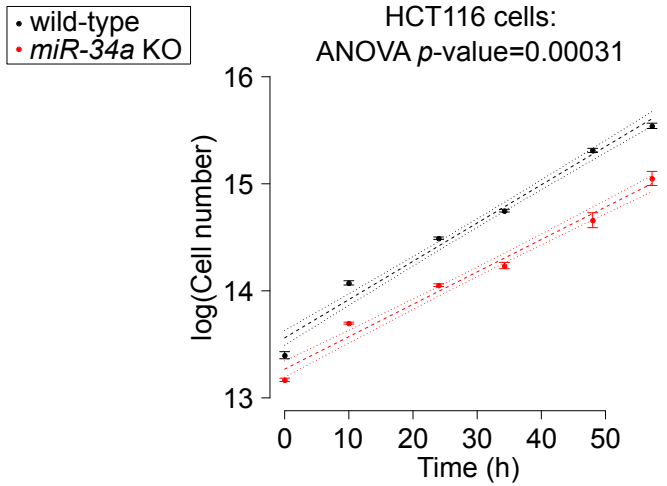

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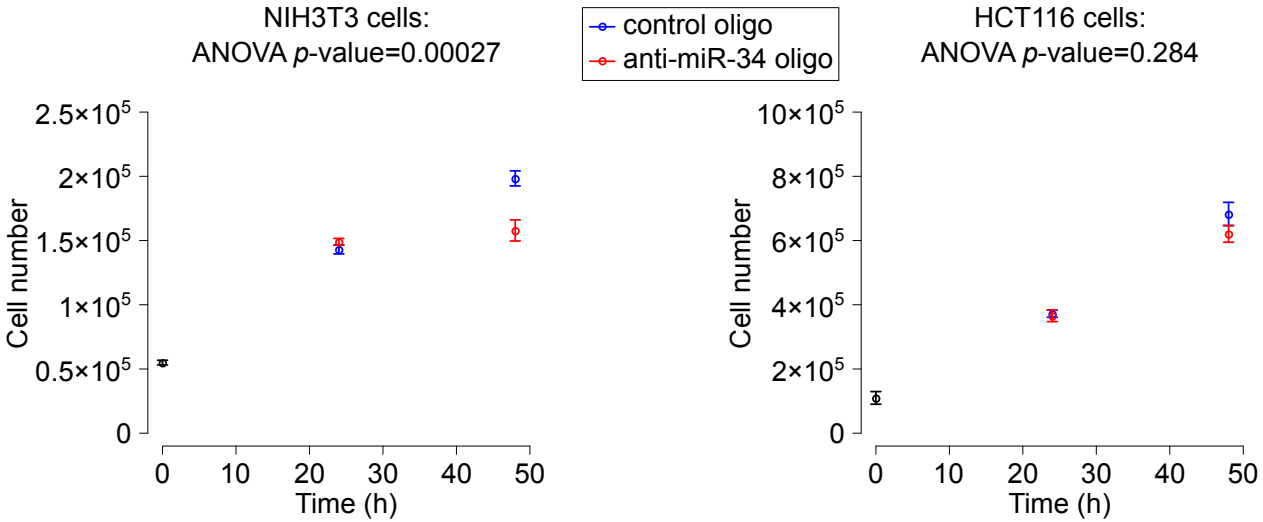

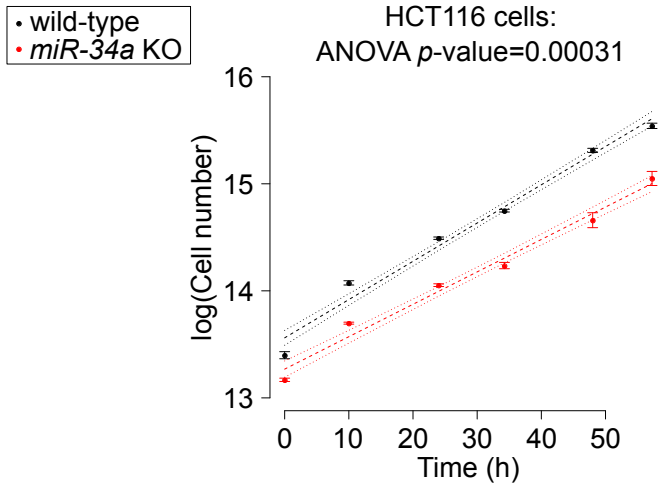

▸ Issues with miRNA over-expression

Conclusion

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

The effect of miR-34 on proliferation could have been mis-understood. Necessity for a proper biological understanding (not piling up long lists of molecular interactors !).

Acknowledgements

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M. Szabo

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Supplementary data

- CLIP and avatars
- Overconservation statistics
- Issues with miRNA over-expression

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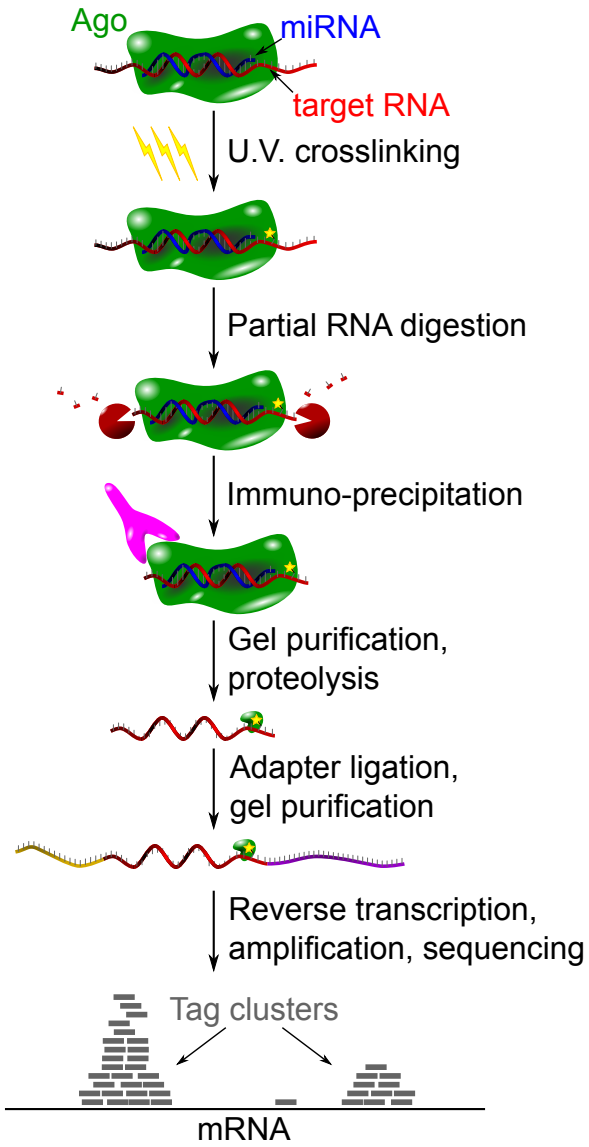

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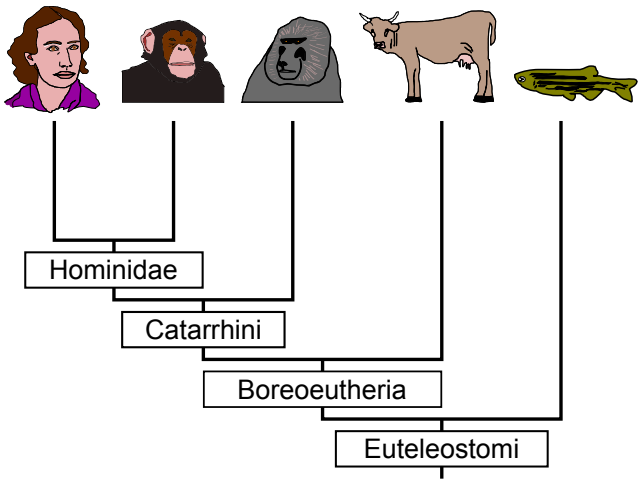

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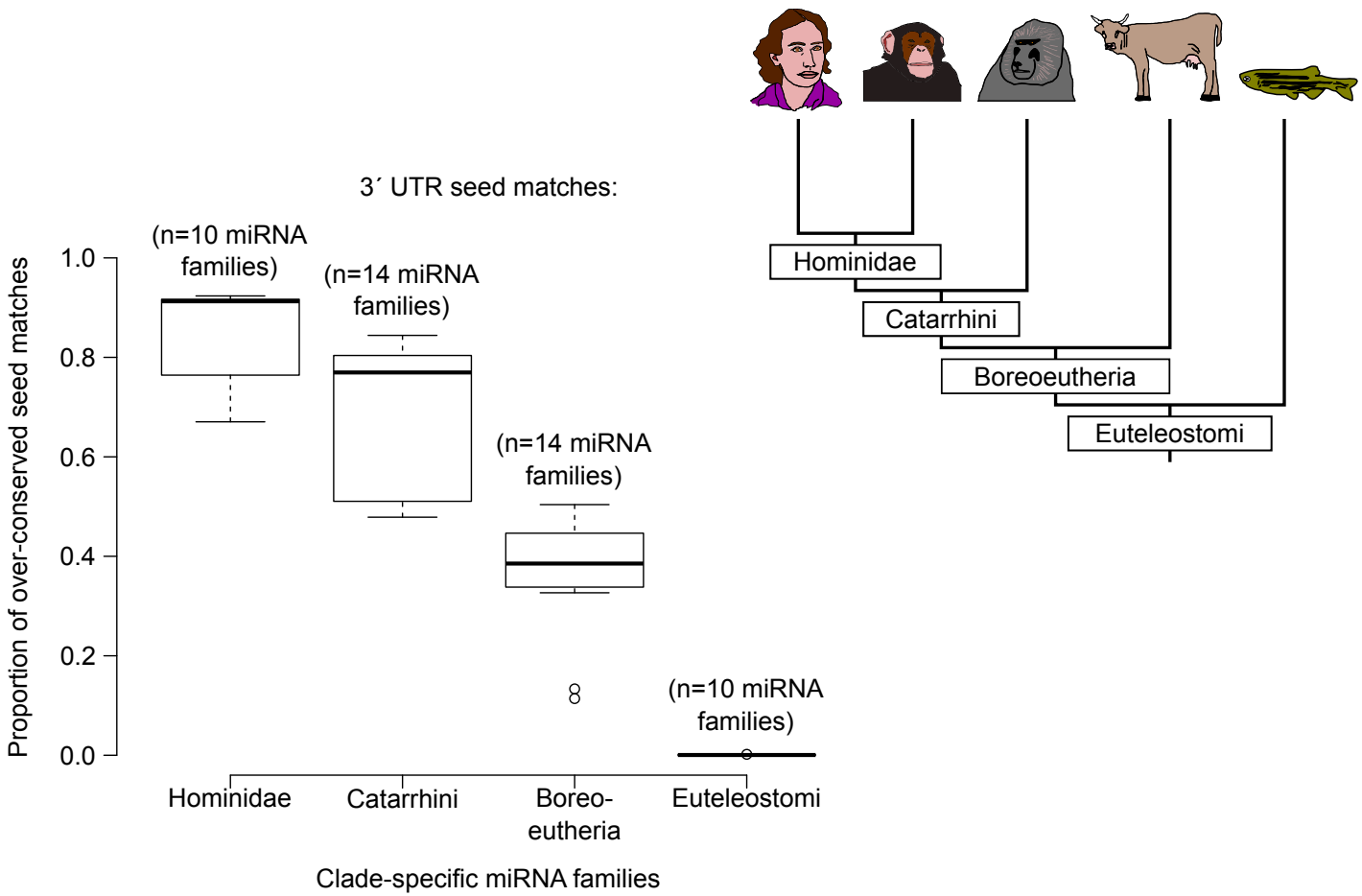
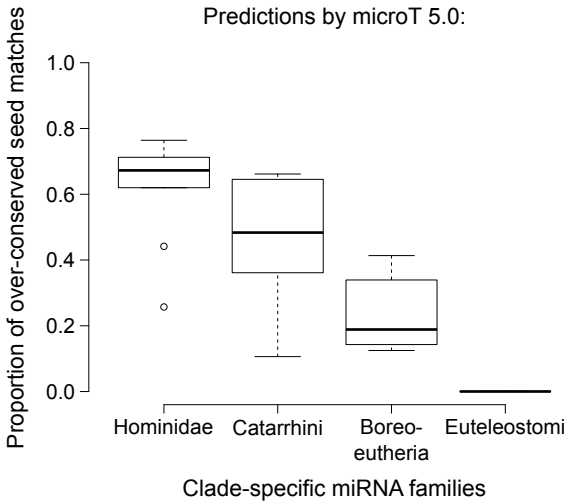


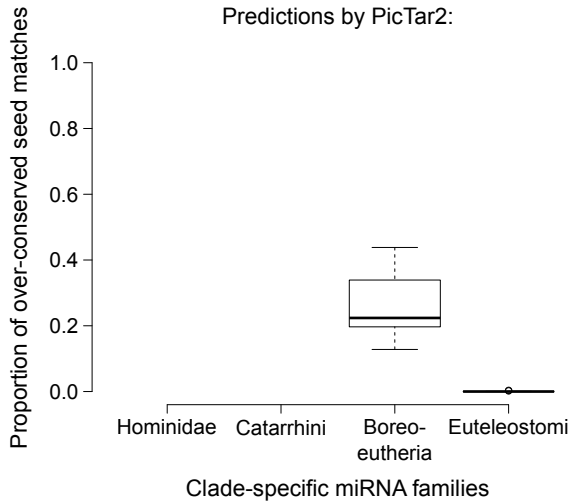
▸ Comparison to prediction programs

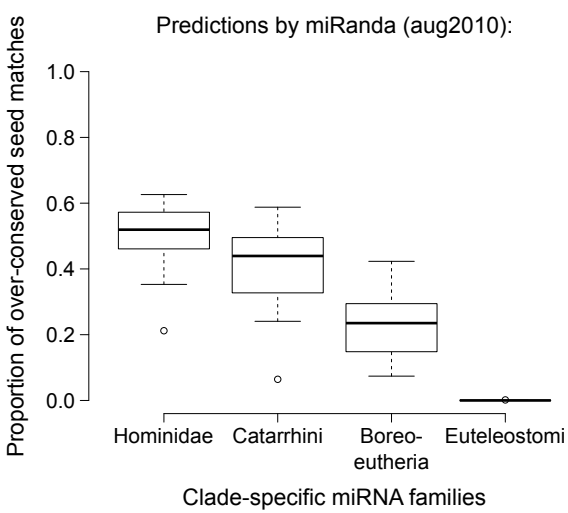
▸ Effect of tree architecture

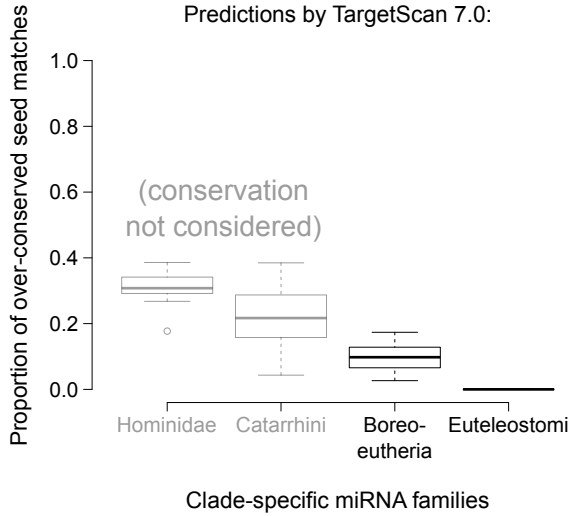
◂ Return

Over-conservation in prediction programs









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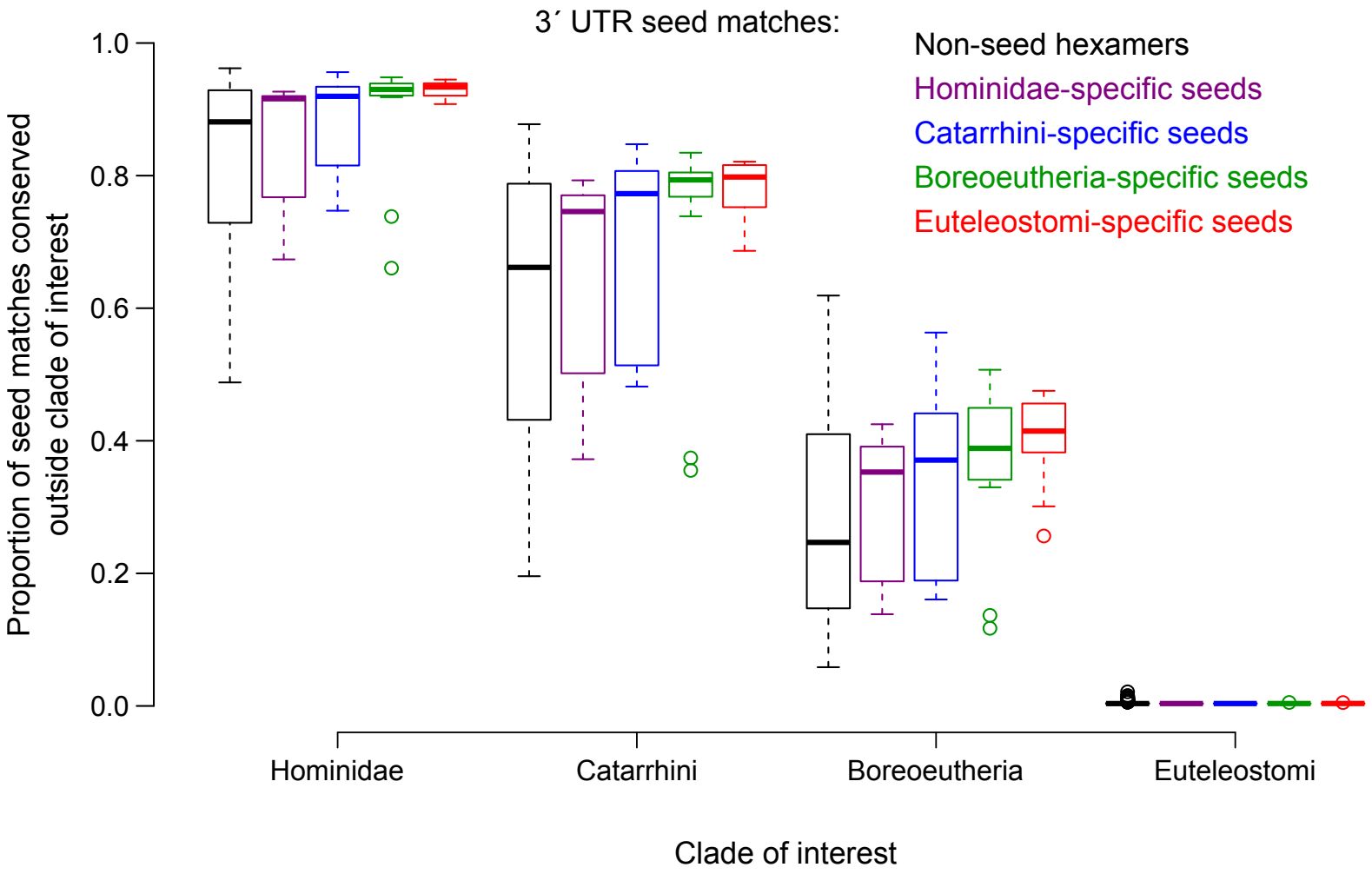
Effect of tree architecture



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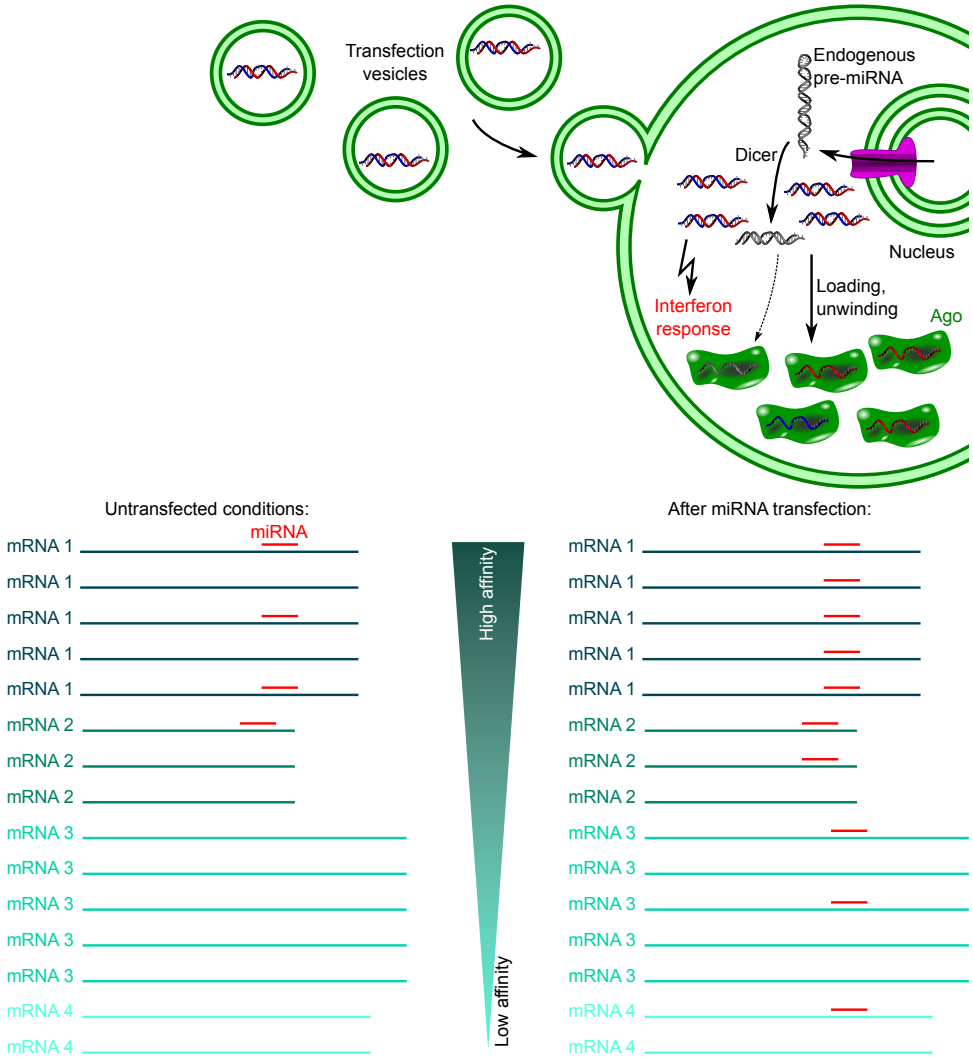
Issues with miRNA over-expression



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