MicroRNA innovations

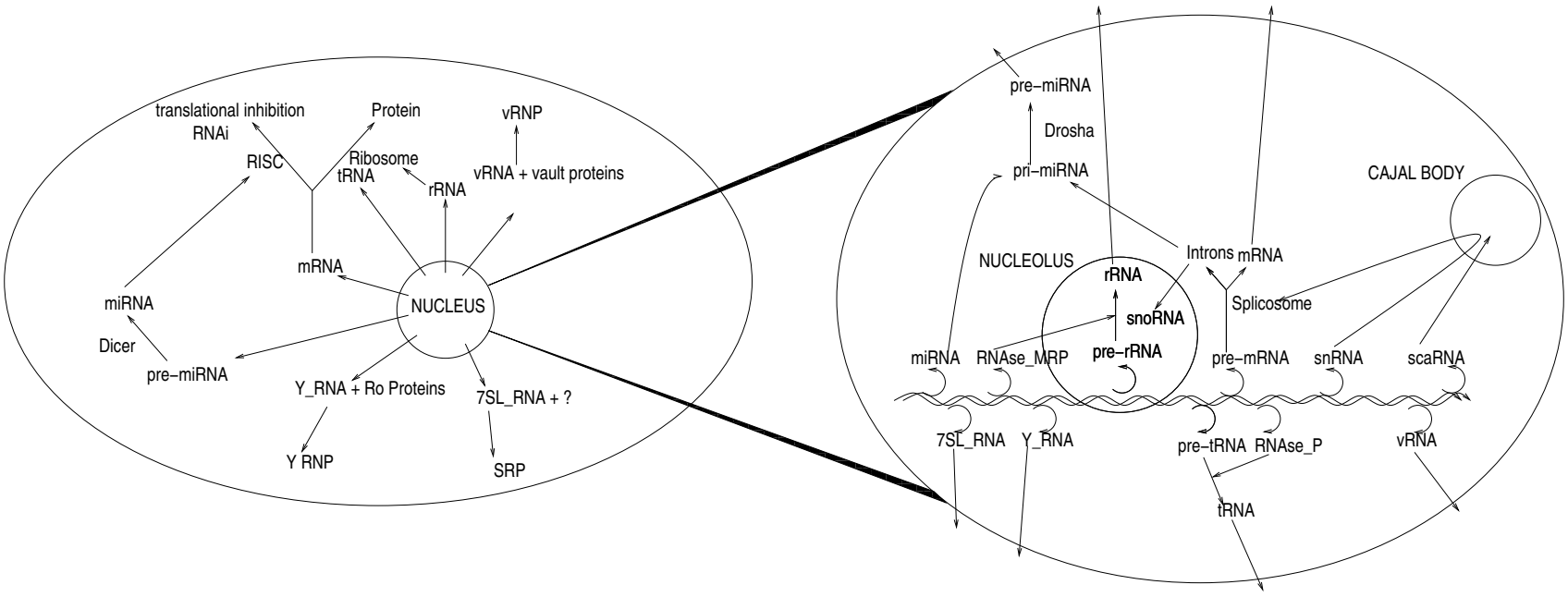
and the origin of novel cell types

A. Tanzer[1,2,3], P.F. Stadler[1,2,4], G.P.Wagner[3]

[1]Bioinformatics Group, Department of Compute Science, University of Leipzig, Germany
[2]Institute for Theoretical Chemistry, University of Vienna, Austria
at@tbi.univie.ac.at
[3]Department of Ecology and Evolutionary Biology, Yale University, New Haven, CT 06511, USA
[4]The Santa Fe Institute, Santa Fe, USA

Bled, Feb 20, 2009

Regulatory RNAs in an Eukaryote Cell



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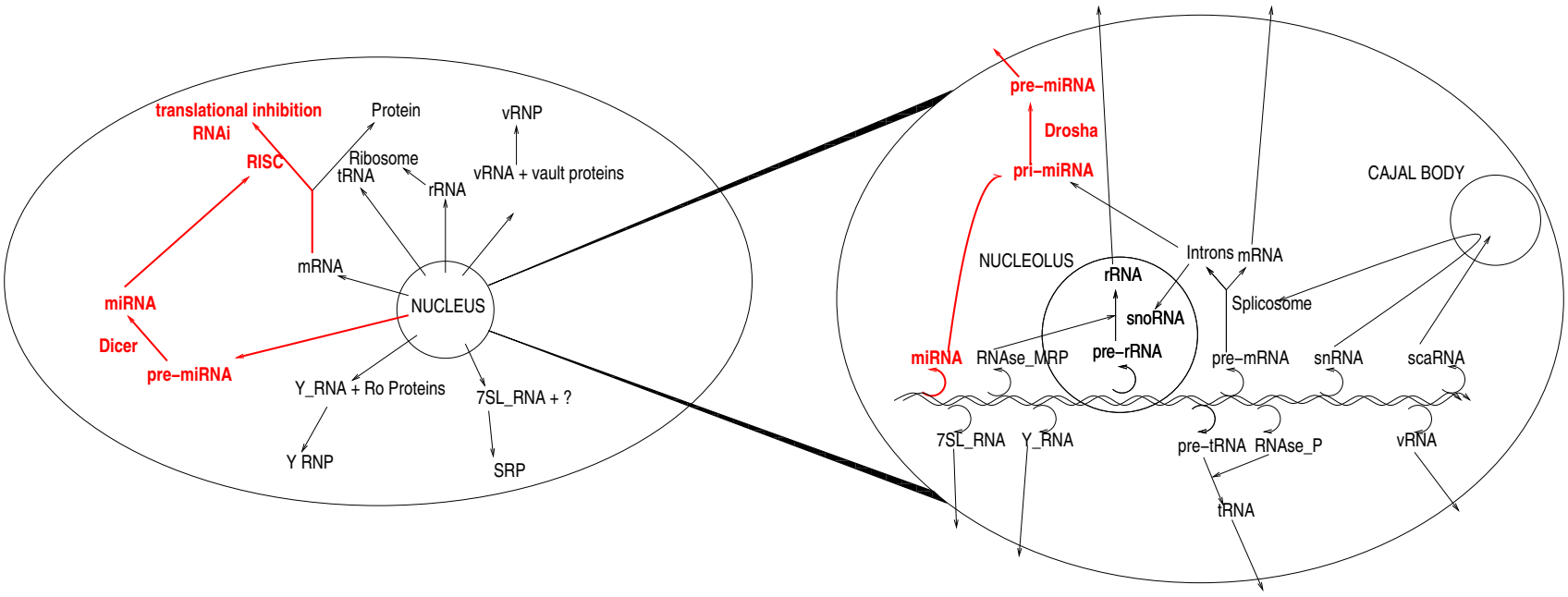
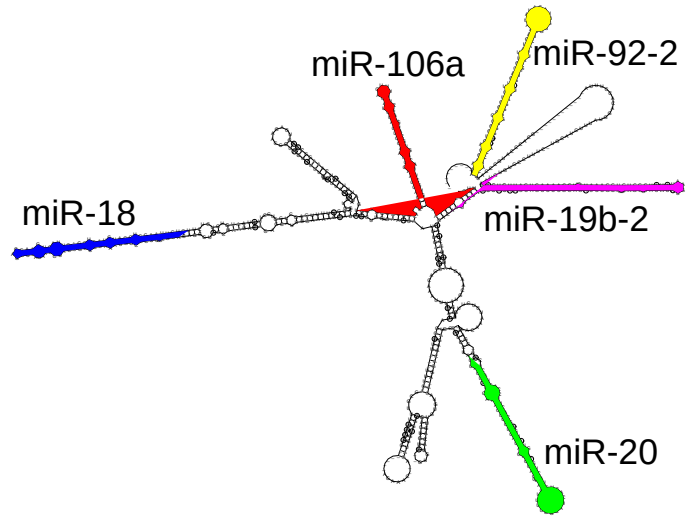


What are MicroRNAs?

- small non-coding RNAs (ncRNAs)
- regulate gene expression
- target DNA and mRNA
- part of protein complexes

Maturation of miRNAs

- primary-precursor micro RNA (pri-miRNA)
- Cleavage I: Drosha
- precursor miRNA (pre-miRNAs)
- export to cytoplasm (exportin-5)
- Cleavage II: Dicer
- mature miRNA (miRNAs)



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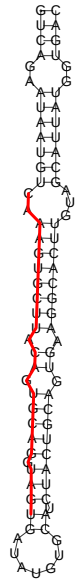

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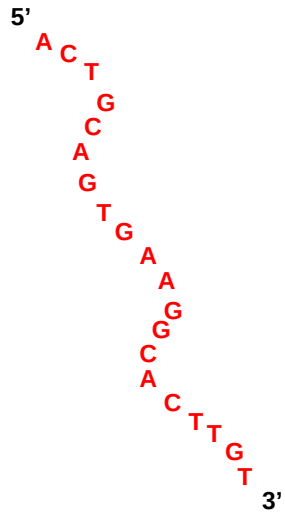

Functions of miRNAs

Cytoplasm: post-transcriptional gene scilencing (PTGS)

- mRNA degradation (RNAi)
- translational repression

Nucleus: transcriptional gene silencing (TGS)

- DNA methylation
- heterochromatin remodelling histone methylation

Nucleus: transcriptional gene activation (RNAa) ?

- binding to promoter regions

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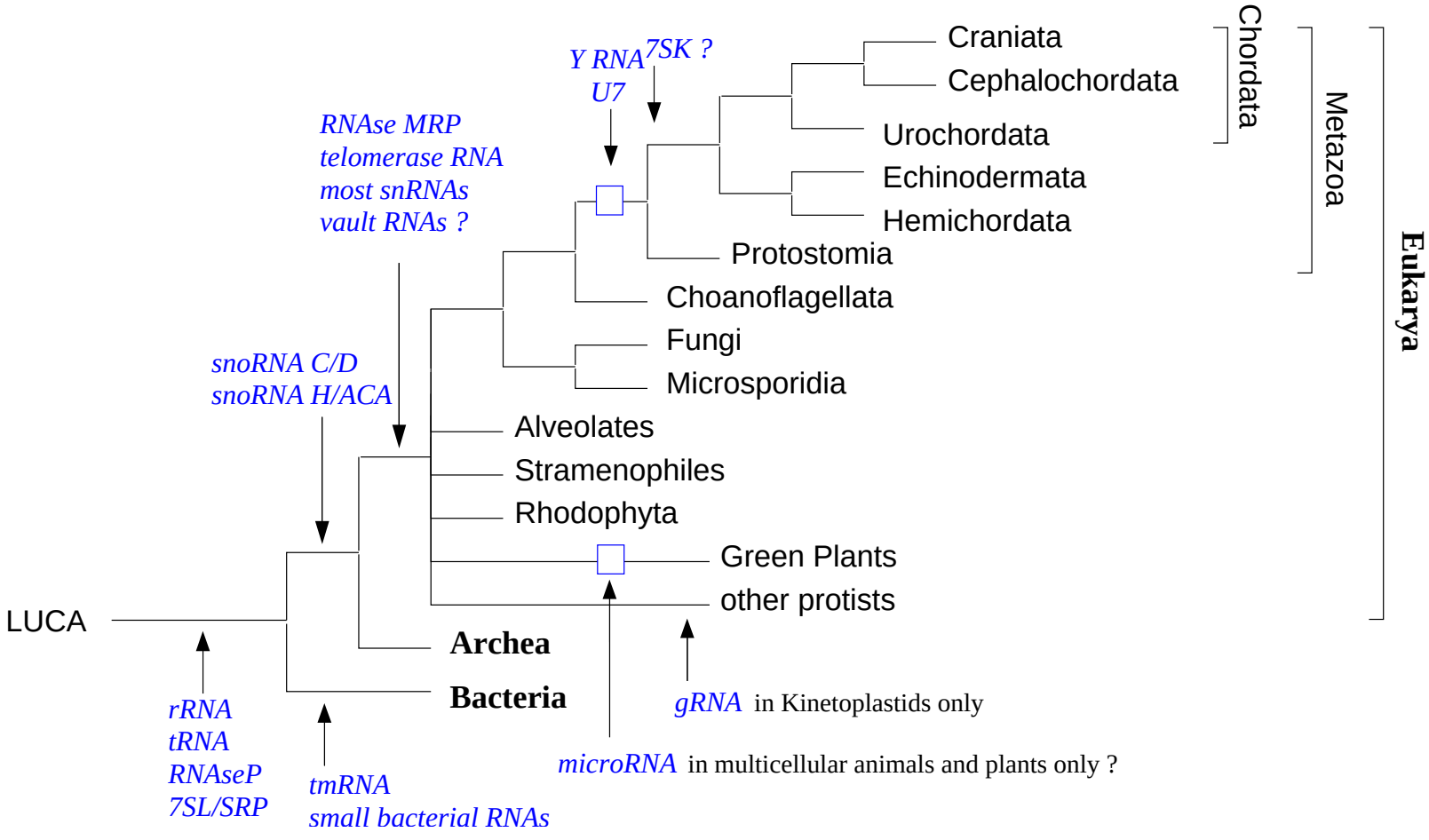
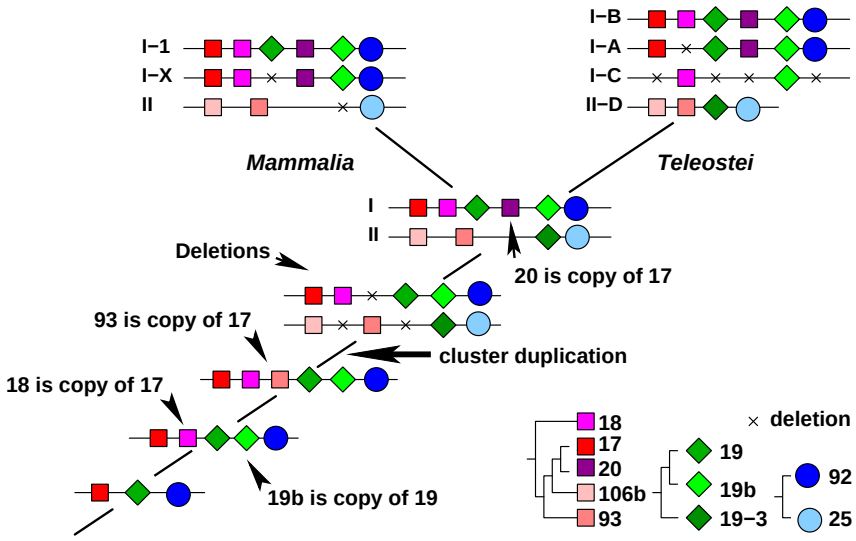
Evolutionary origin of prominent ncRNA families



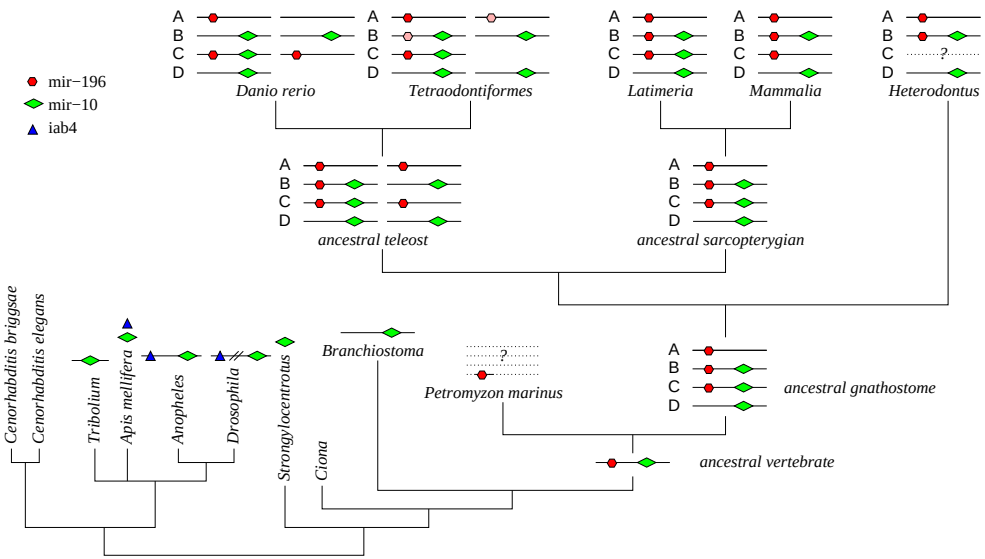
Molecular Evolution of selected miRNAs

mir-17 cluster



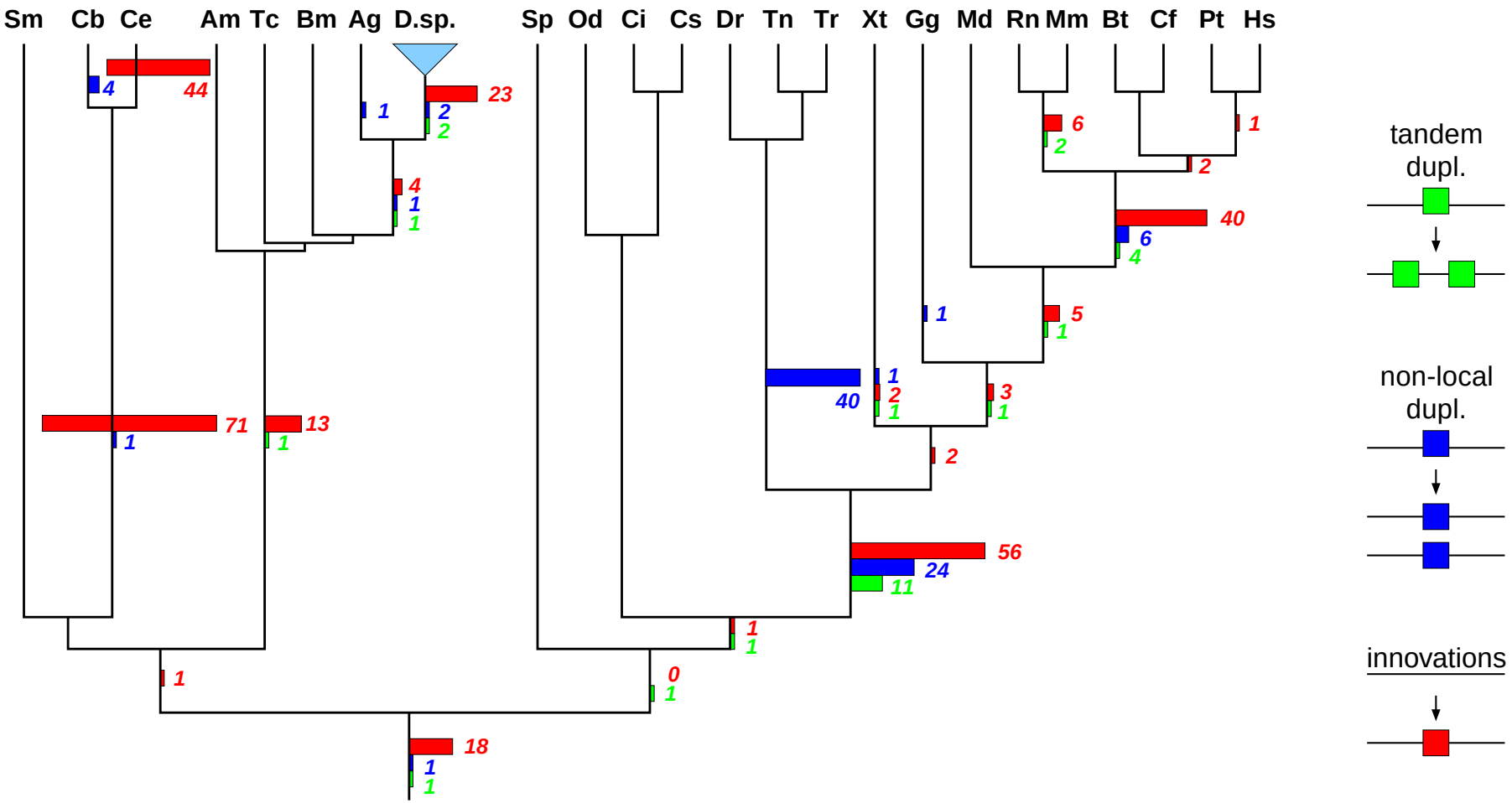
Tanzer and Stadler. J Mol Biol. 2004; 339:327-35

mir-10, mir196, iab-4 in the Hox gene cluster



Tanzer *et al.* J Exp Zoolog B Mol Dev Evol. 2005; 304:75-85

Expansion of The Metazoan MicroRNA Repertoire



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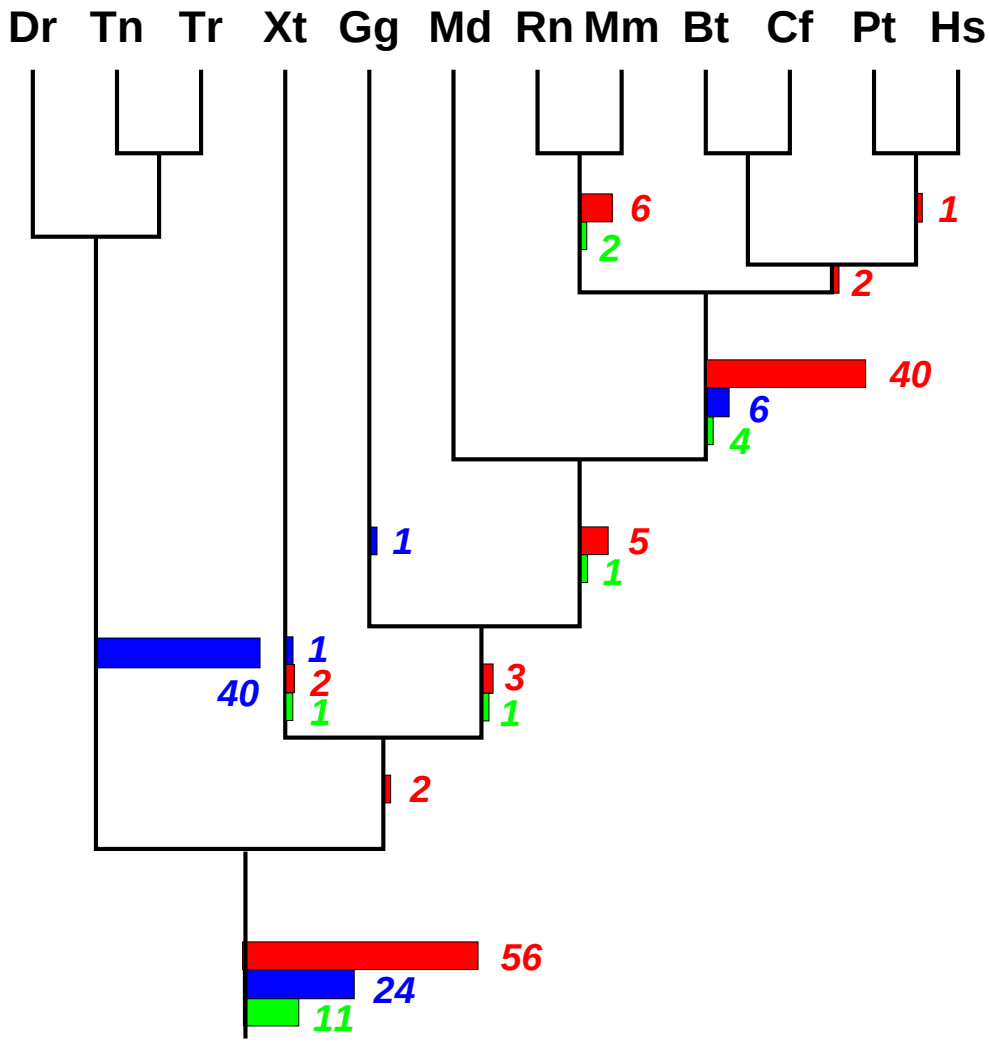

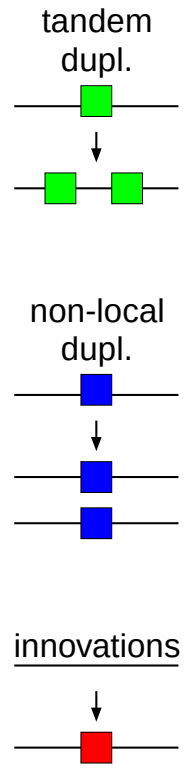

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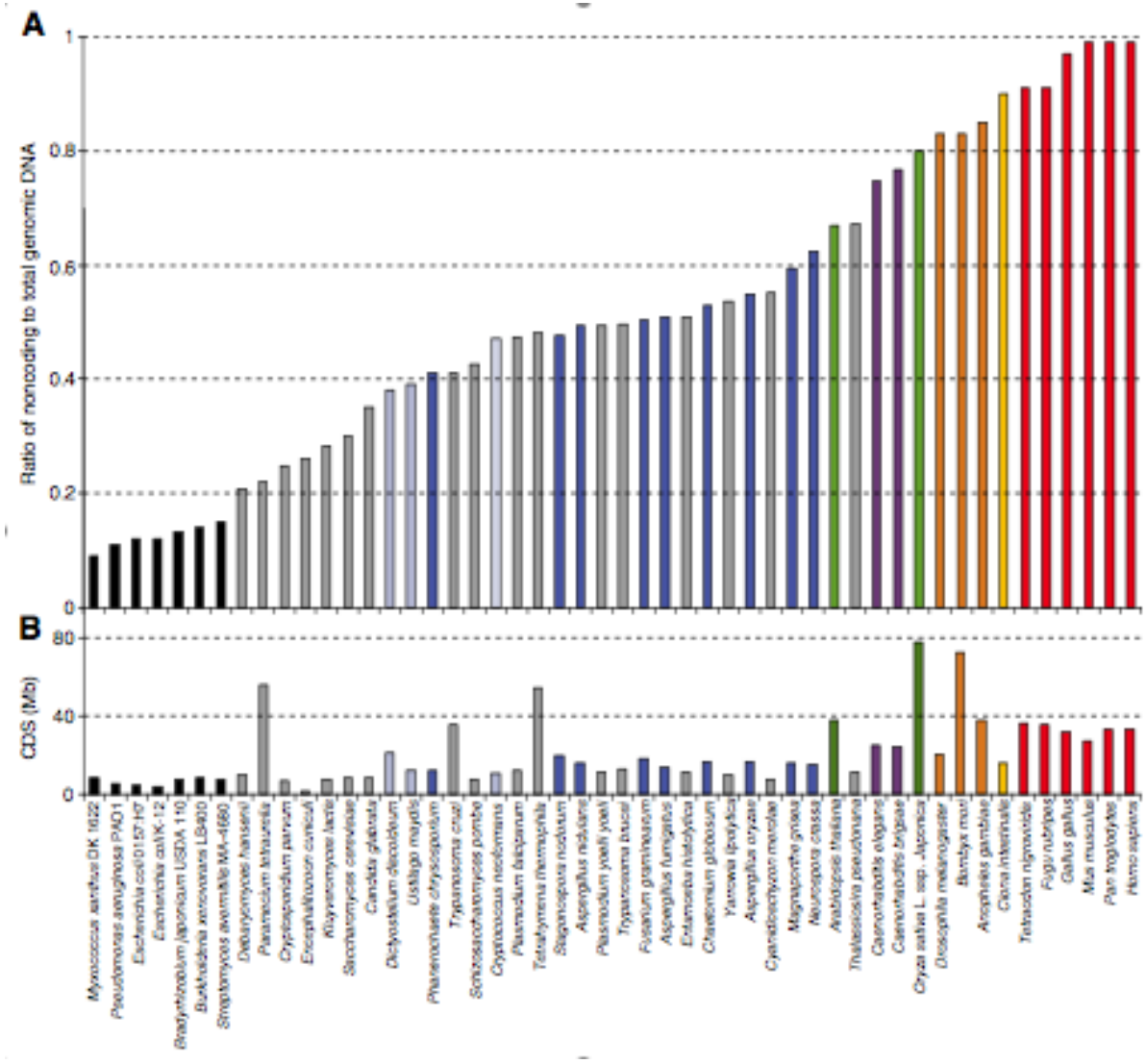
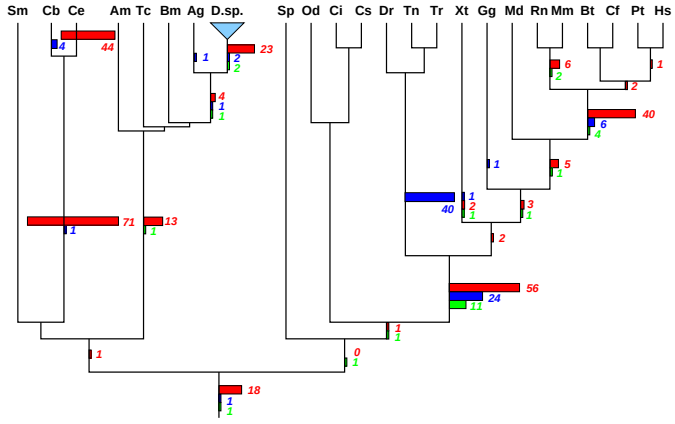
Genomic Complexity



Mattick JS, The Journal of Experimental Biology 210, 1526-1547

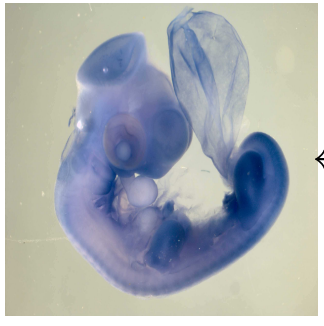
MicroRNAs in Developmet



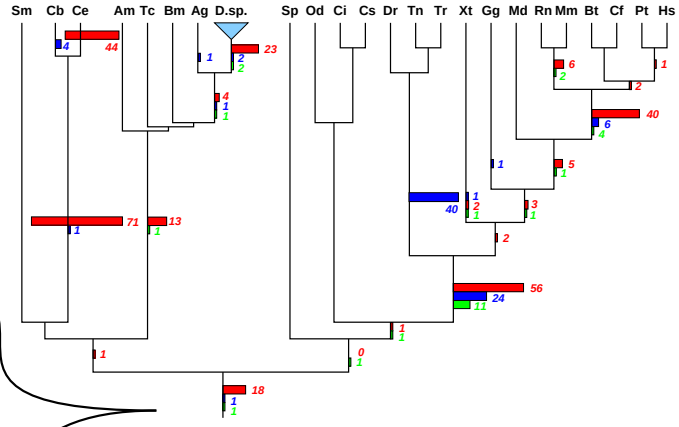
chicken: http://geisha.arizona.edu/, zebrafish: http://exiqon.com/

MicroRNAs in Developmet

mir1: heart, somites



mir10b: limb buds



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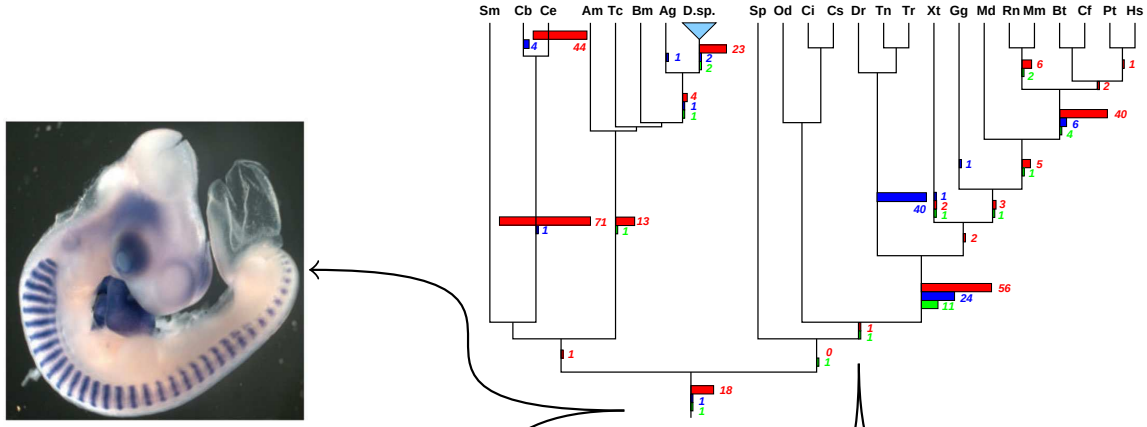

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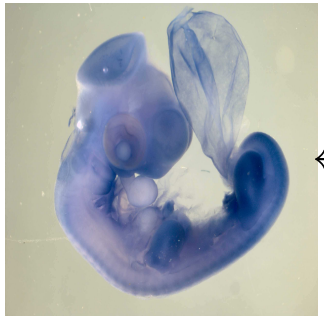

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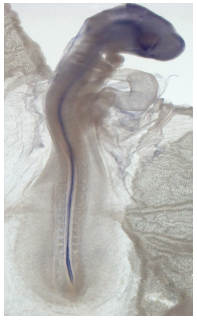

mir140:spinal cord

mir140: cartillage

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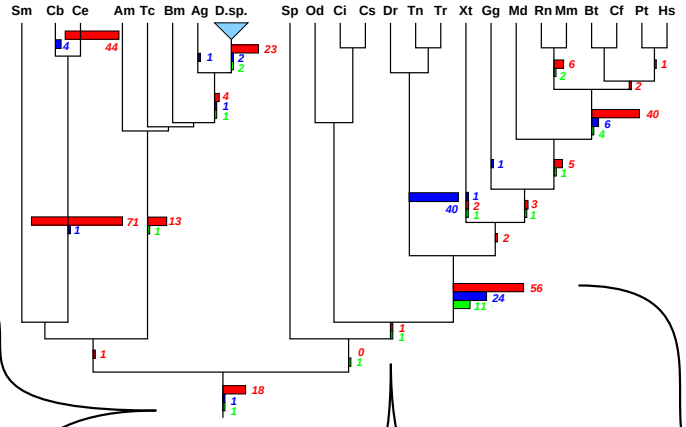

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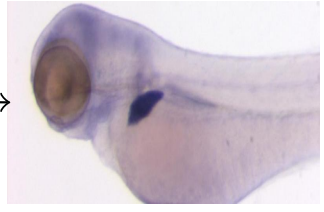
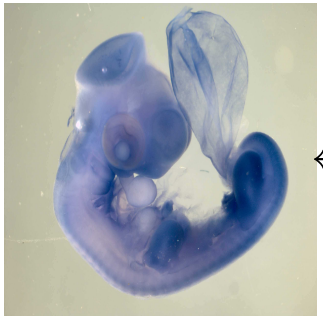


mir122: liver



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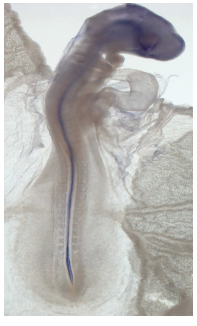

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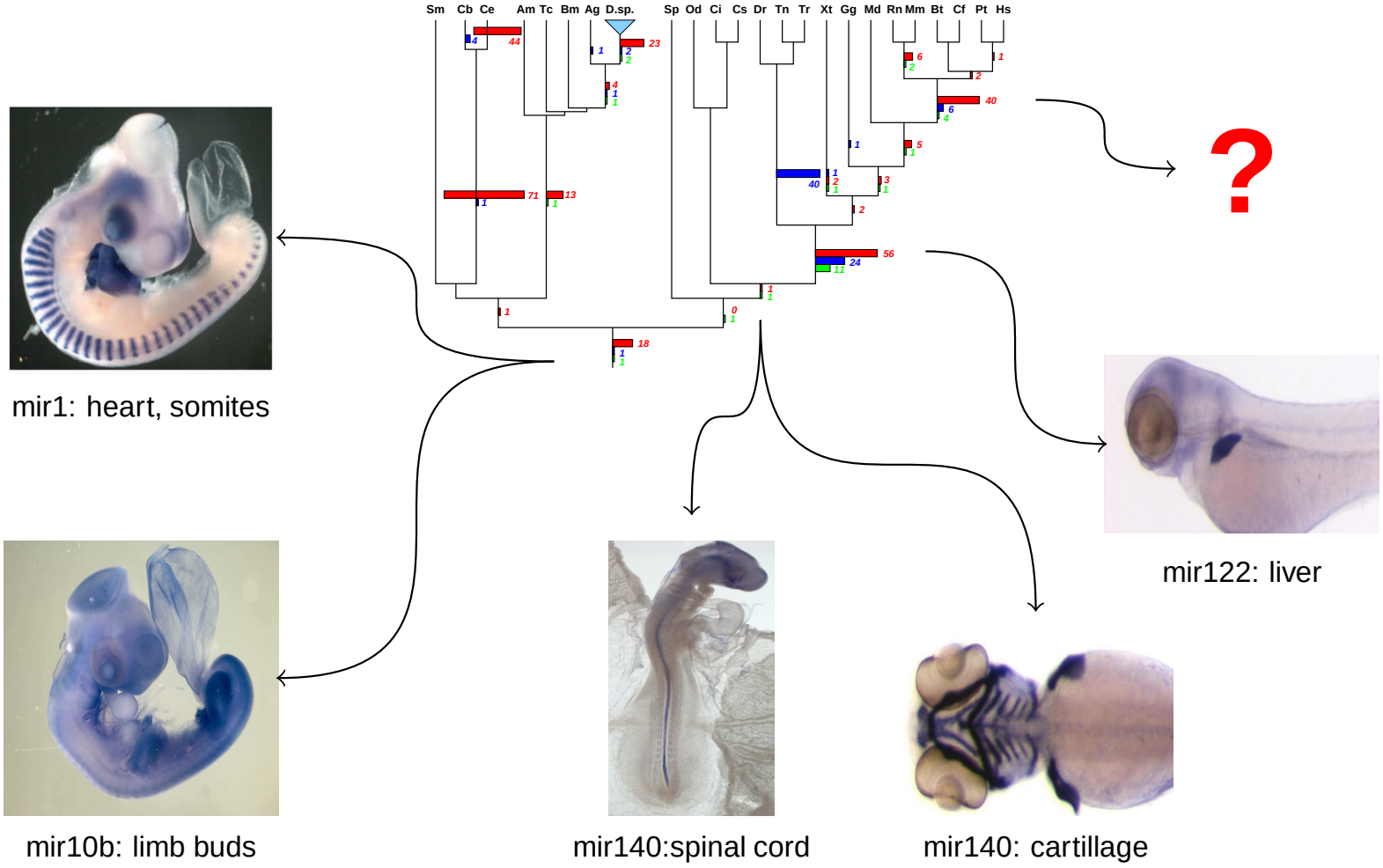

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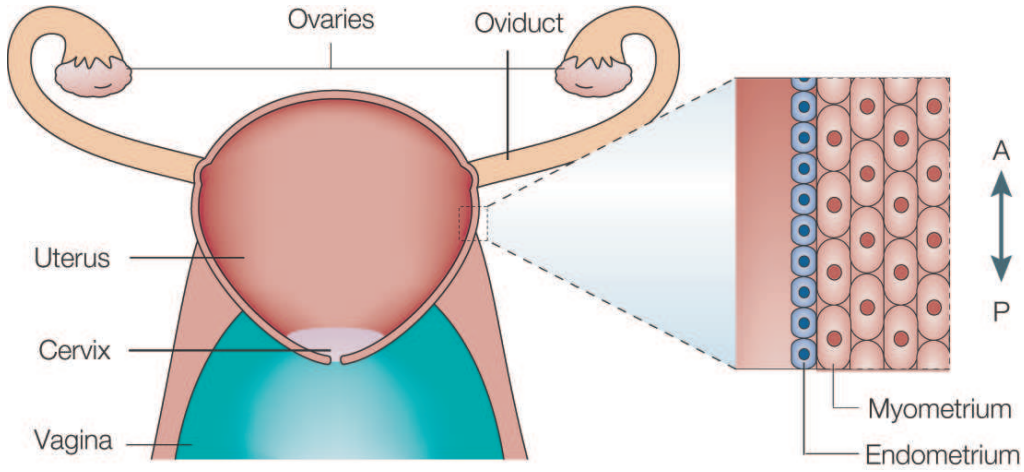
Novel Cell Type in Eutherian Mammals: Endometrium

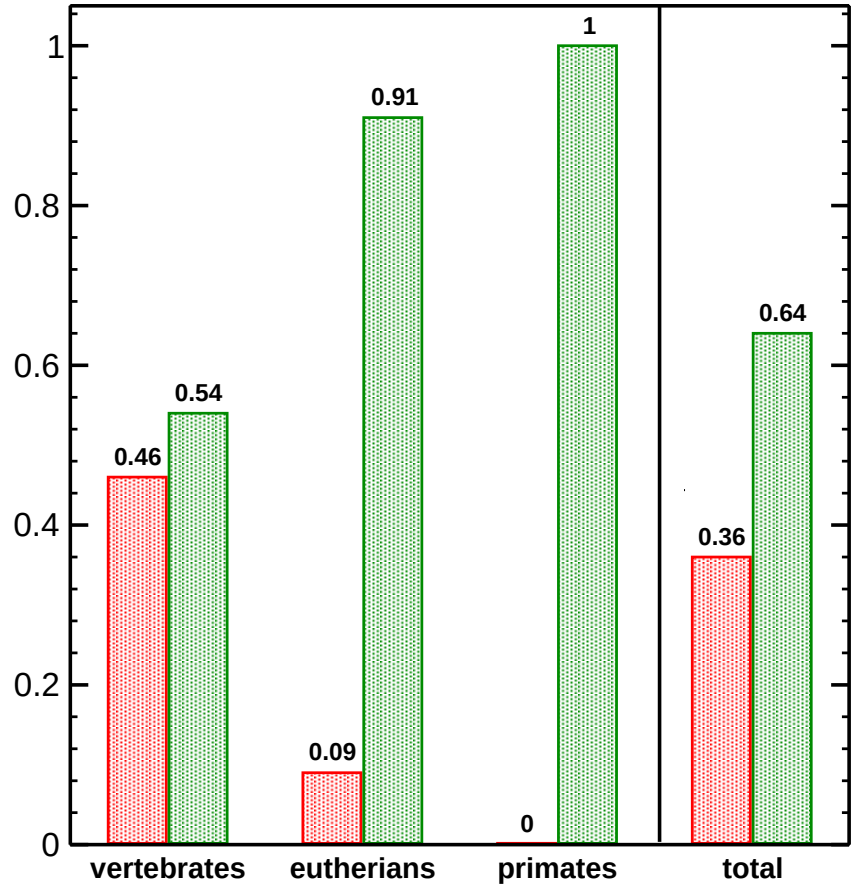


- inner layer if the uterus
- implantation and decidualisation
- differentiation induced by progesterone and estrogen

adapted from: Kobayashi, A and Behringer, R R, Nat Rev Genet (2003), 4:969-980

MicroRNA expression analysis: Microarray

- majority expressed upon homon treatment
- vertebrate miRNAs act in both diff. and undiff cells
- eutherian and primate miRNAs highly upregulated in diff. cells



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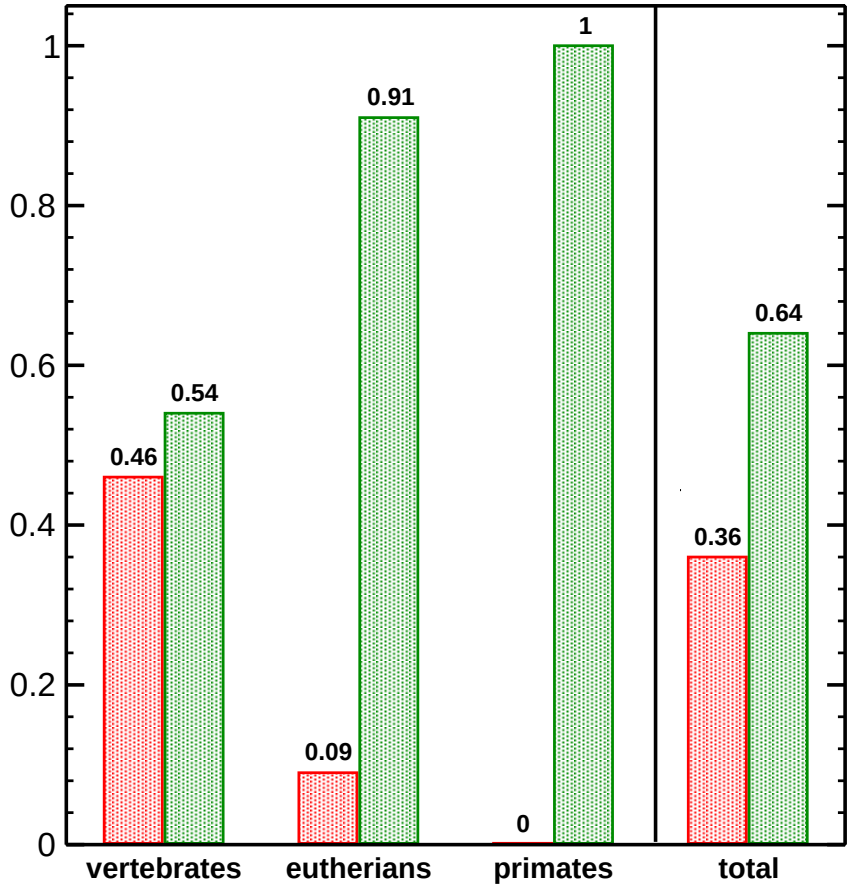

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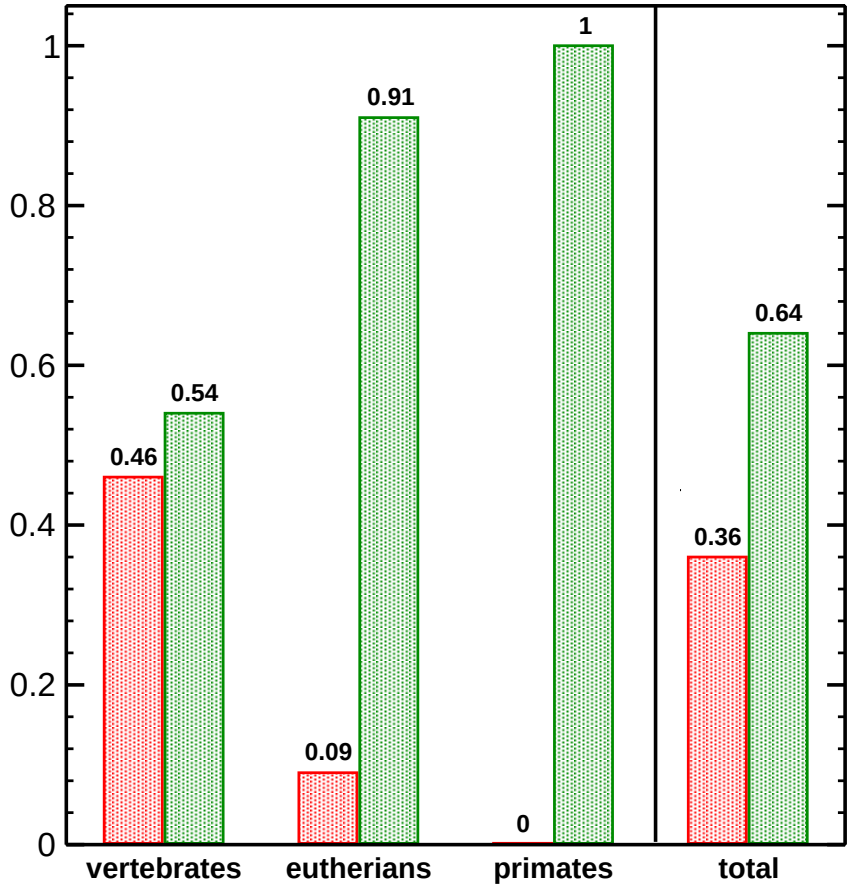
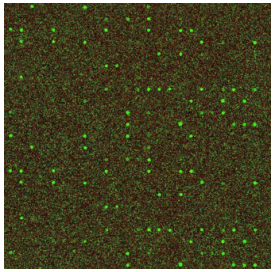
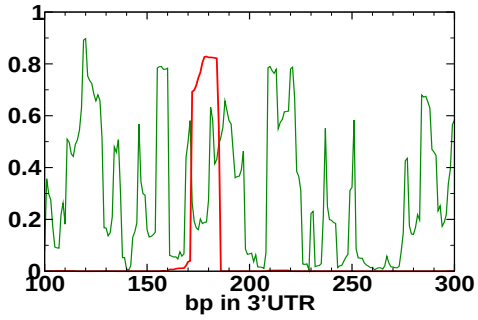


Functional study: miRNA knock downs

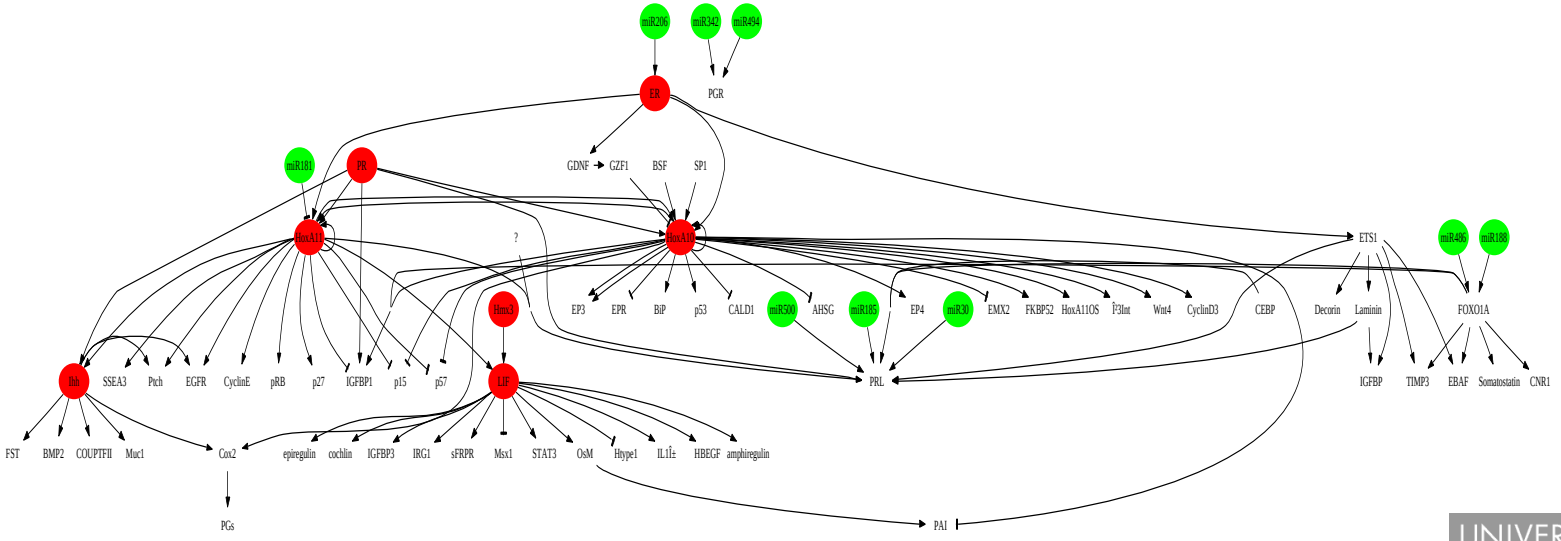
mirVana miRNA microarray



RNAup target predictions



Gene regulatory network in endometrial stromal cells



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- miRNA are cool
- evolution of miRNAs still an ongoing process
- waves ob innovation - major transition in body plan formation
- novel miRNAs expressed in novel tissues
- ncRNA repertoire linked to complexity of organism
- are we ribo-organisms?

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