miR-34a is not a tumor suppressor

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Slideshow accessible for download at:
http://www.igh.cnrs.fr/equip/Seitz/CRCT21.pdf

Defining “gene regulation”

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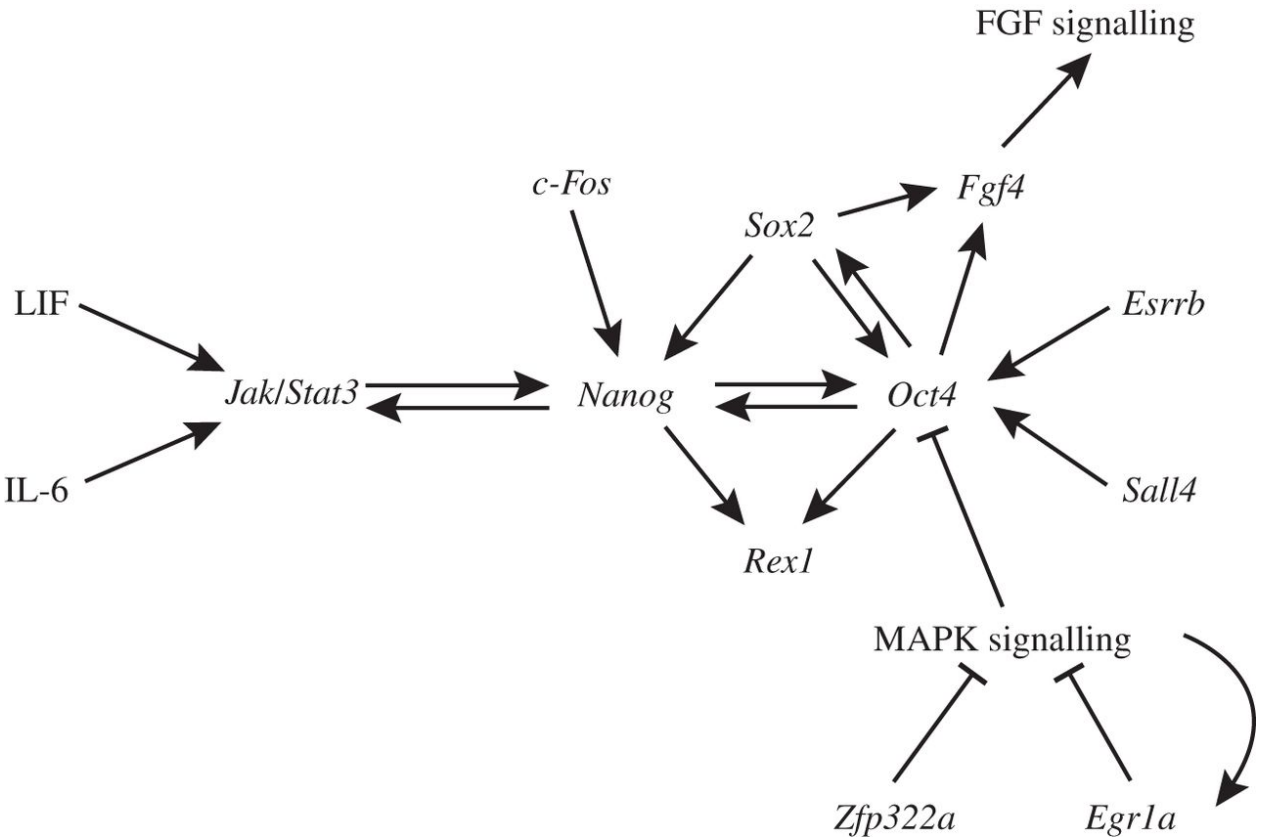

(Parfitt and Shen, 2014)

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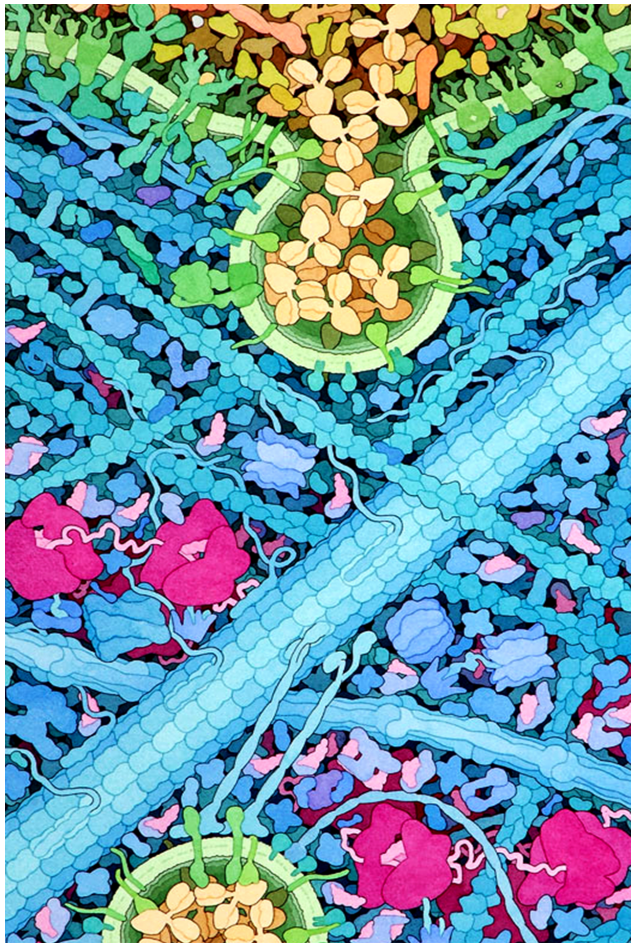

(illustration by D. Goodsell, Scripps Research Institute and Rutgers University)

microRNAs

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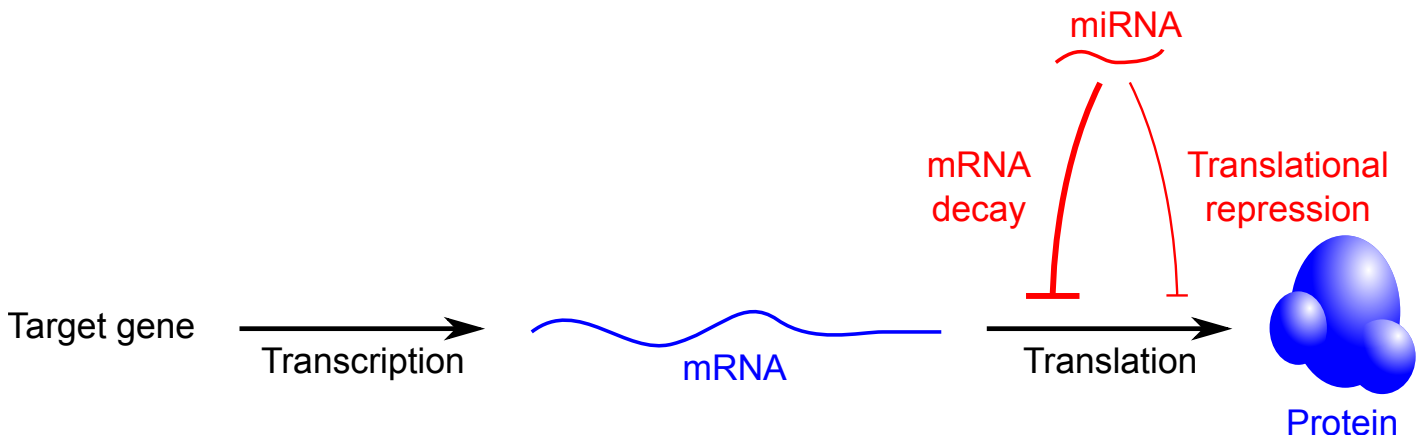

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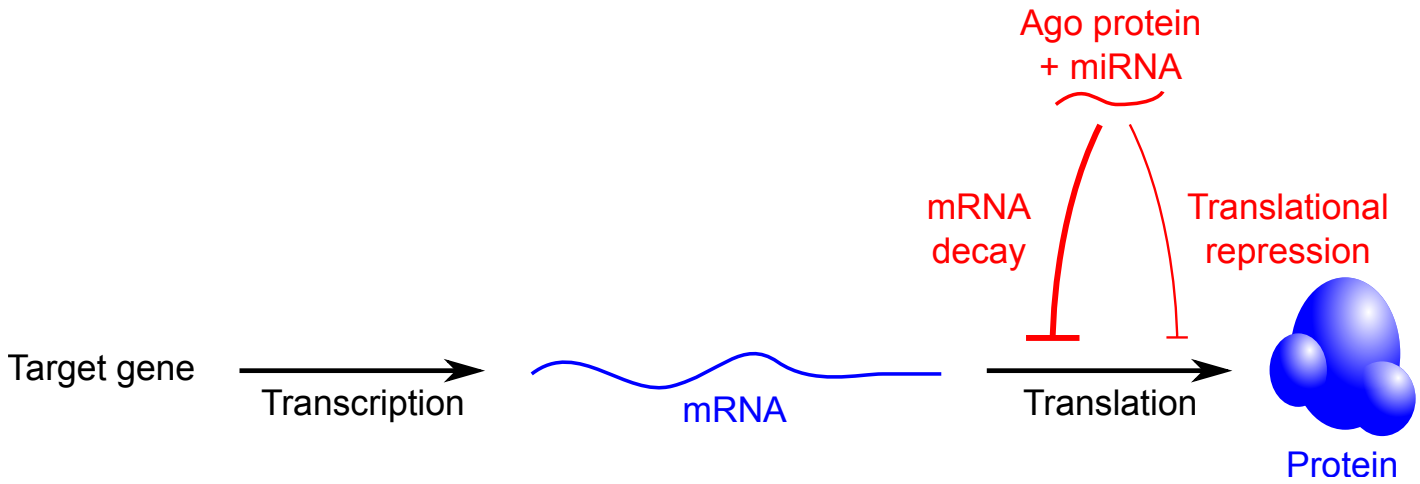

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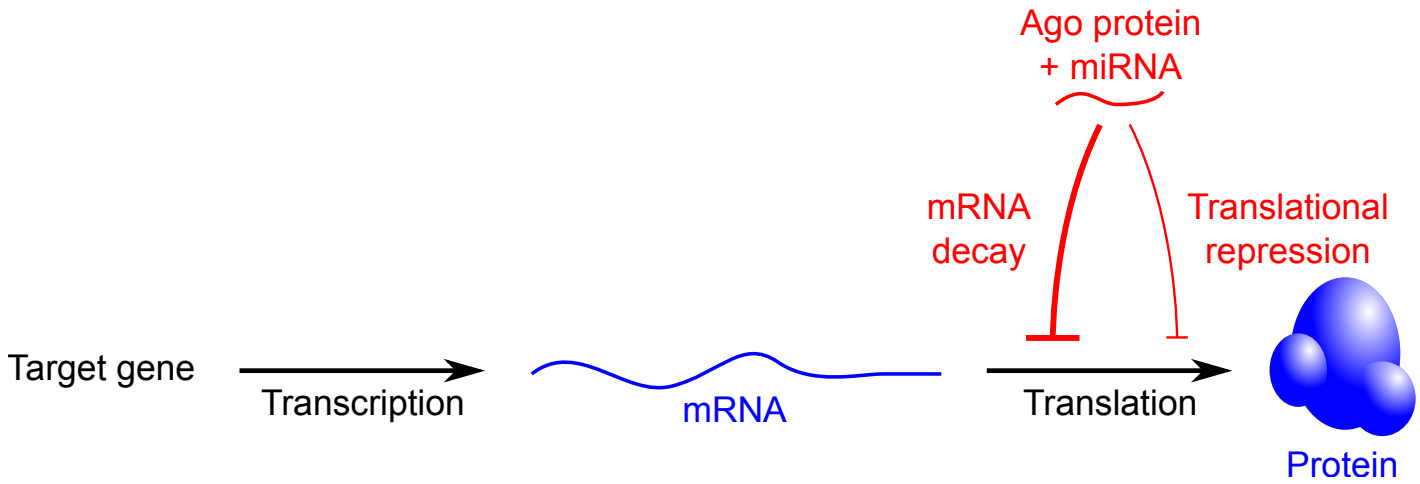

miRNA sequences are known (for the most part); can we identify their targets ?

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  - ▸ CLIP protocol
- mRNA and protein level respond to miRNA.
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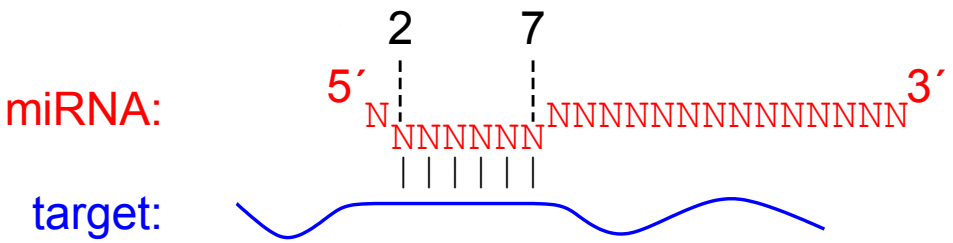

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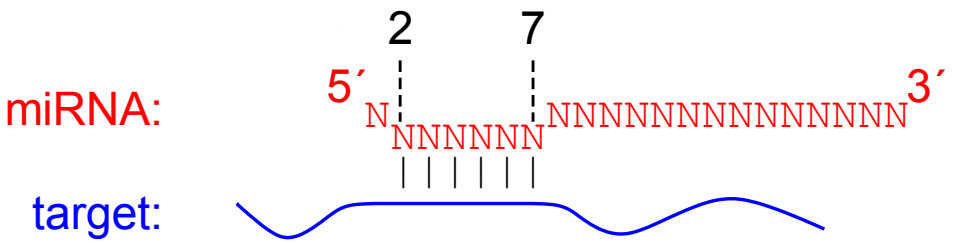

$\longrightarrow$ the "seed"

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.
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Both experimental and computational target prediction methods capture mostly false positives (Pinzón *et al.*, 2017).

miR-34 in cancer

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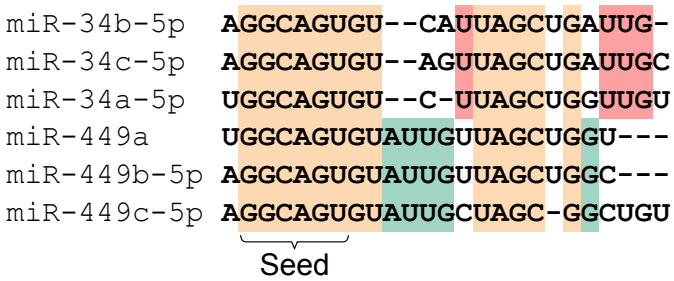
Human miR-34 family members:



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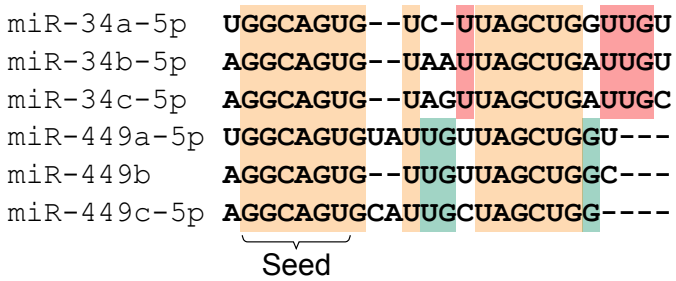

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miR-449a     UGGCAGUGUAUUGUUAGCUGGU---
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             ^^^^^^^
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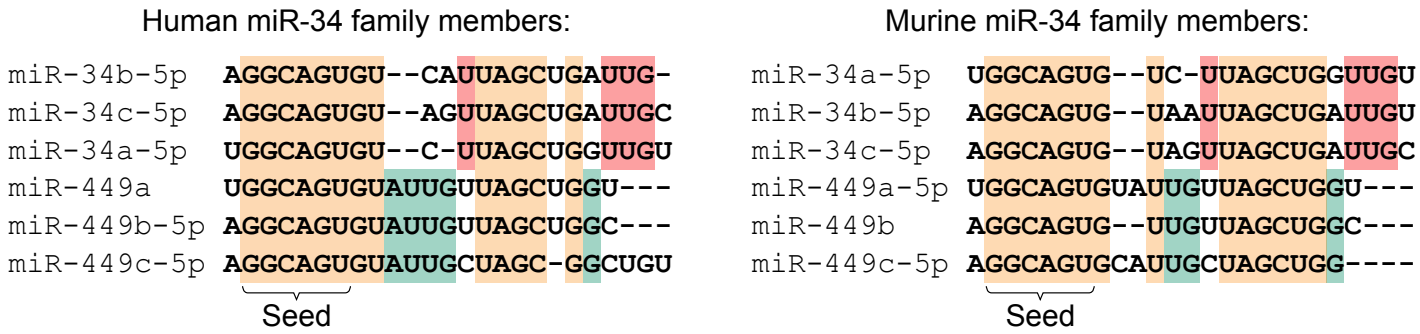

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$\longrightarrow$ *miR-34a*, first described tumor-suppressing miRNA.

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Problems:

- In mouse, a triple KO (miR-34a, b and c) and a sextuple KO (miR-34a, b and c and miR-449a, b and c) do not have increased cancer frequency (Concepcion *et al.*, 2012; Song *et al.*, 2014).

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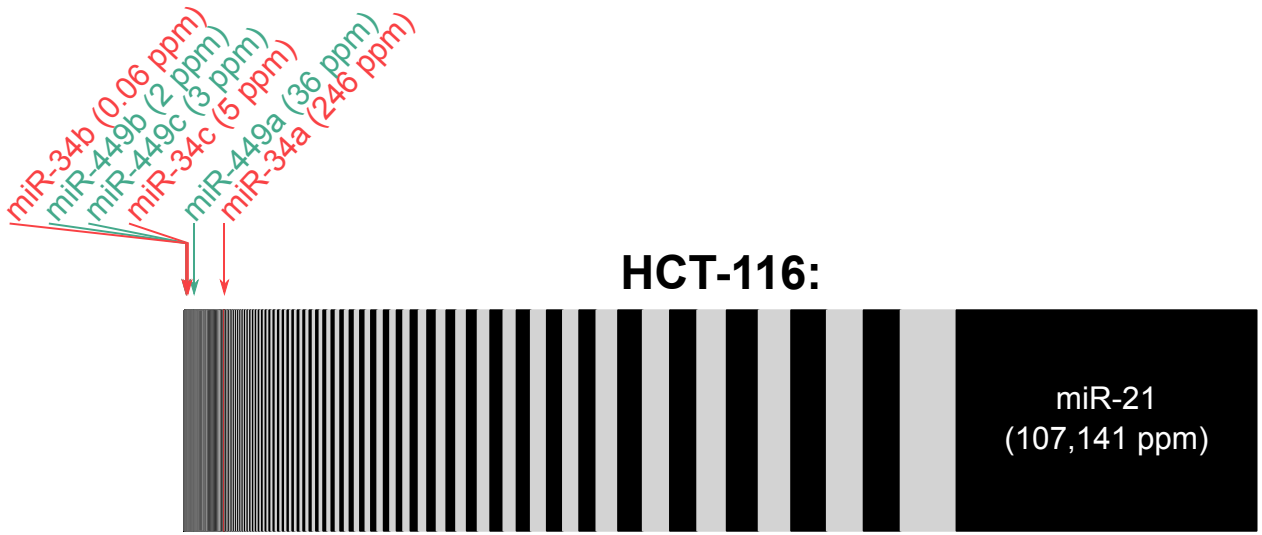

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▸ Additional cell lines, tissues and body fluids

Poorly-expressed miRNAs fail to repress their targets, while being easily detectable (Mullokandov *et al.*, 2012).

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- miR-34 miRNAs are poorly expressed in most cells.
- MRX34 clinical trial failed to improve cancer patients' condition.

miR-34a is not a general repressor of proliferation

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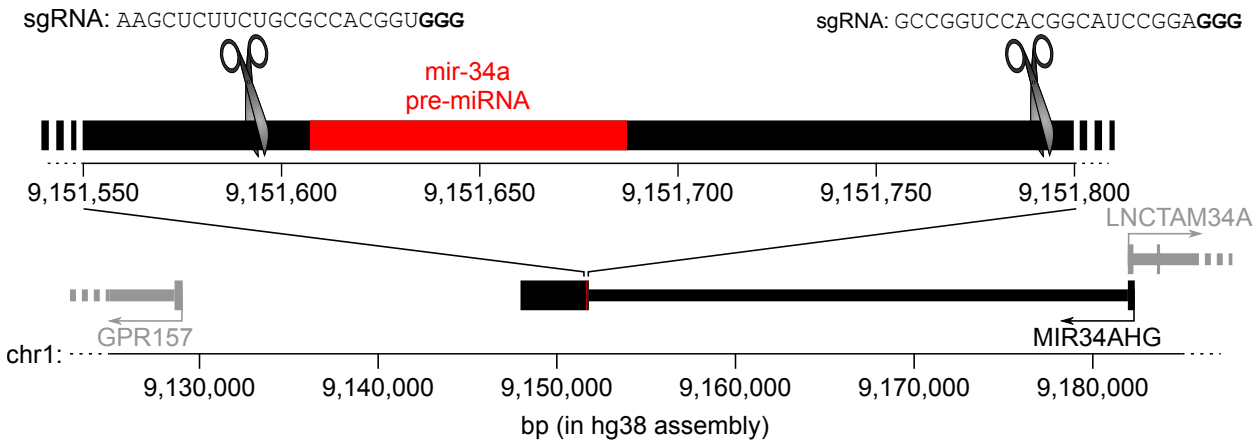
In human HCT-116 and HAP1 cells:



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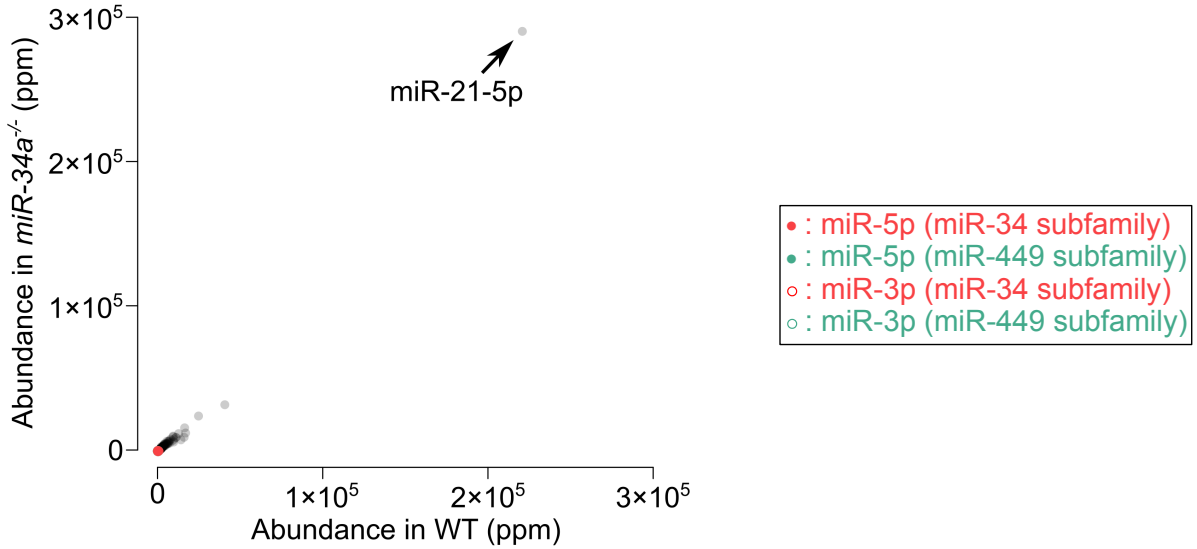

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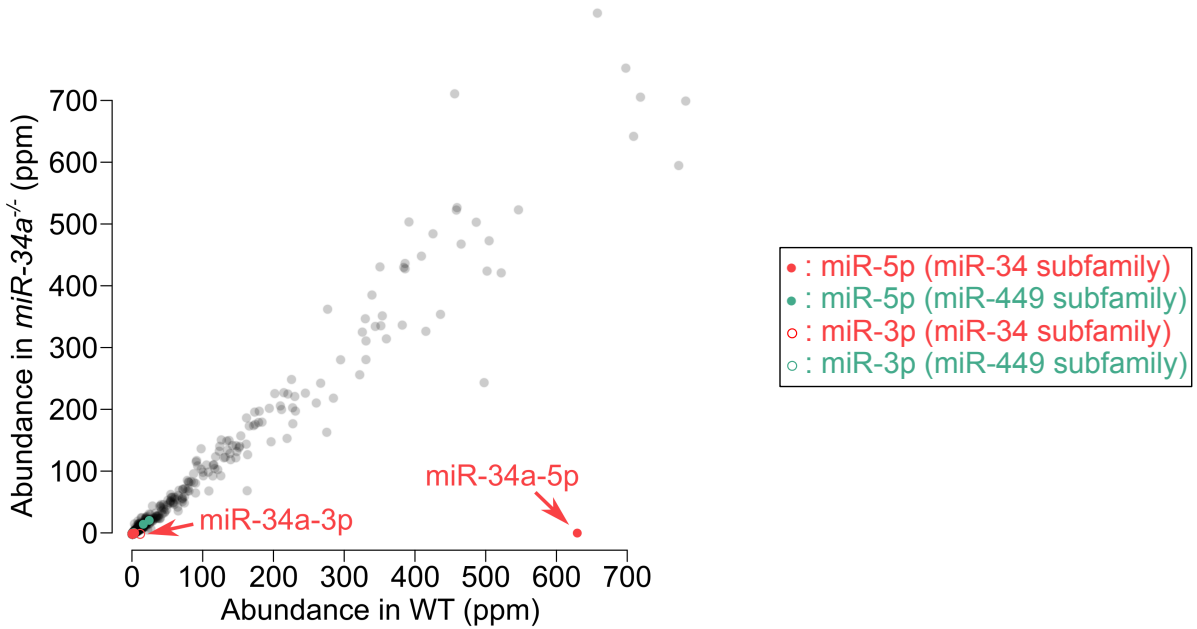

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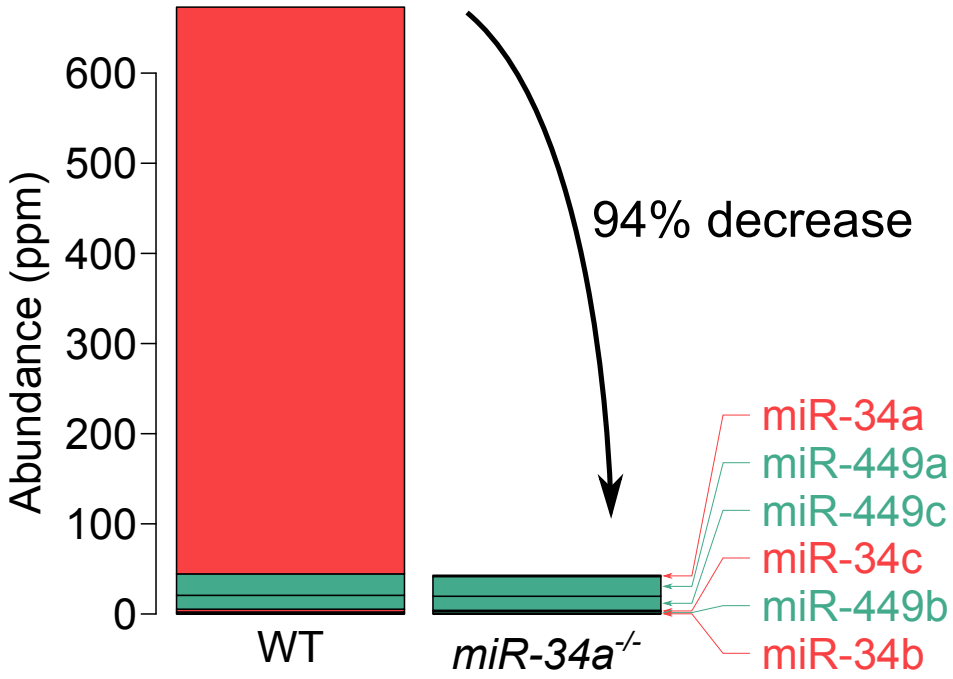

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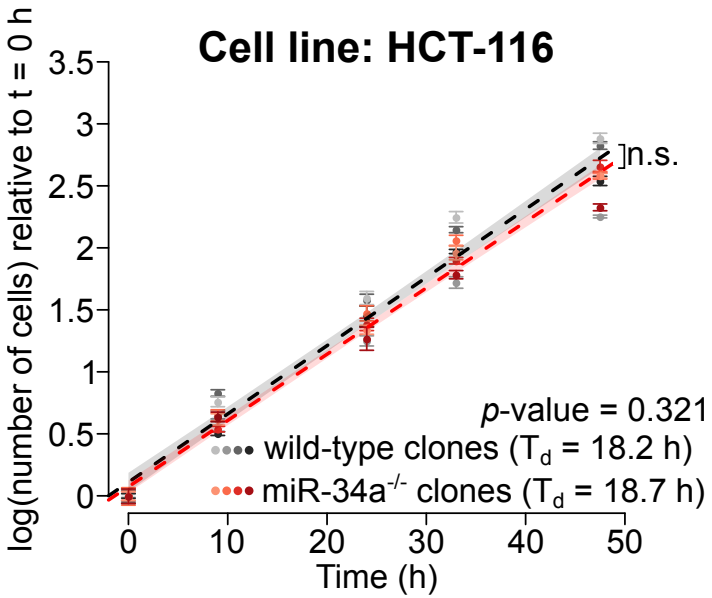

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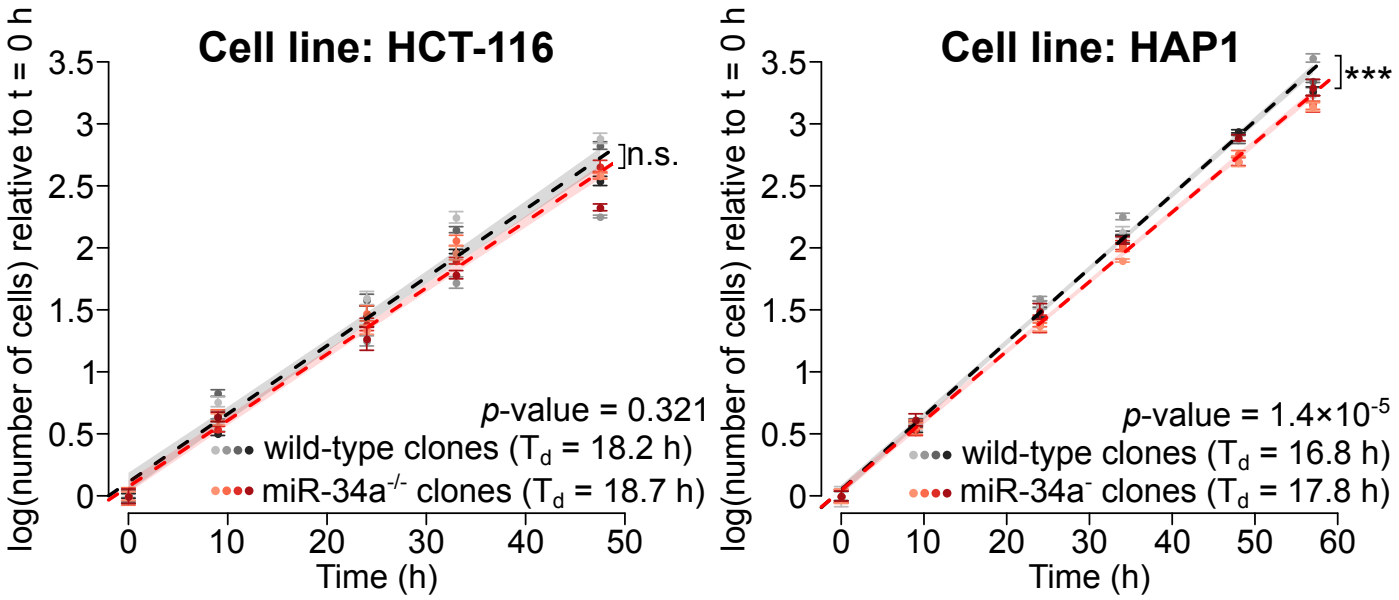

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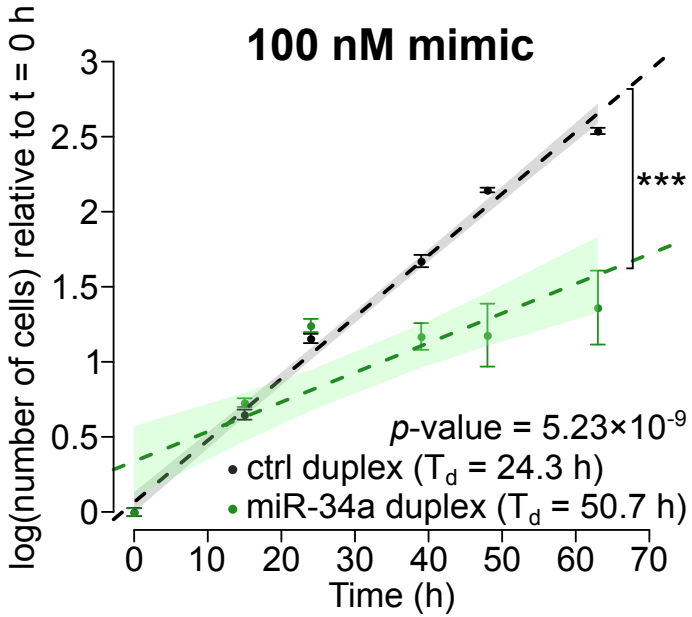

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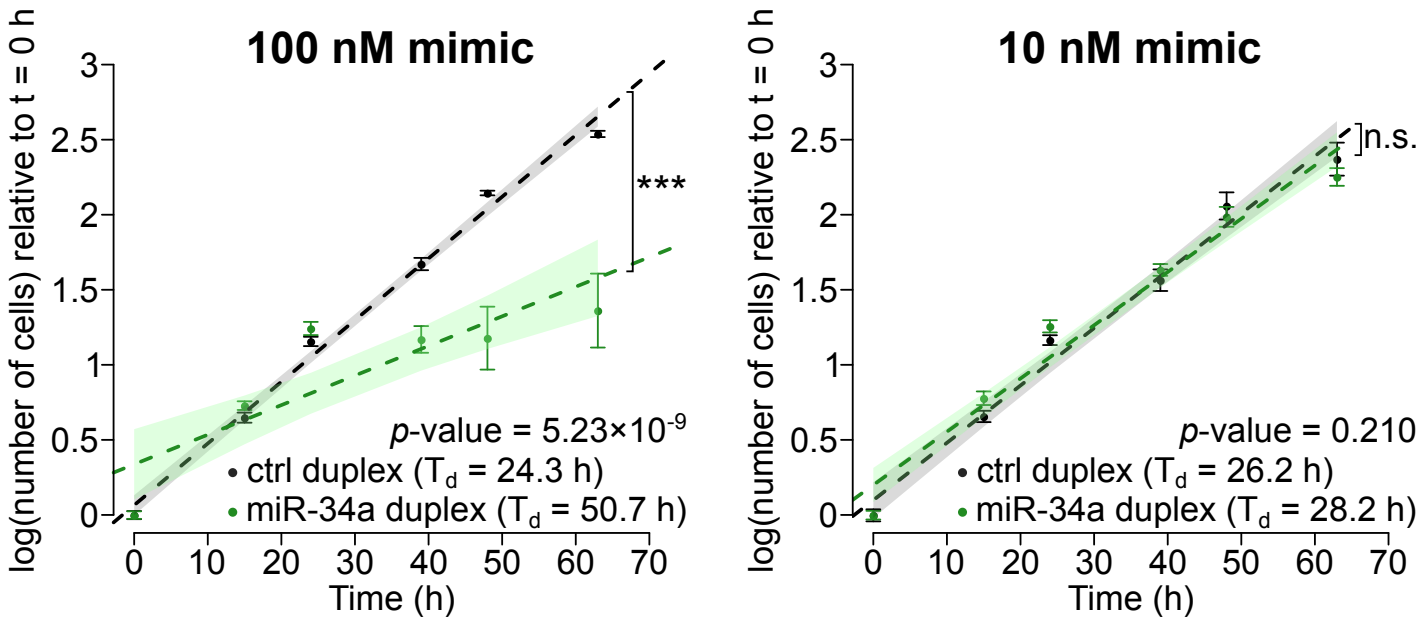

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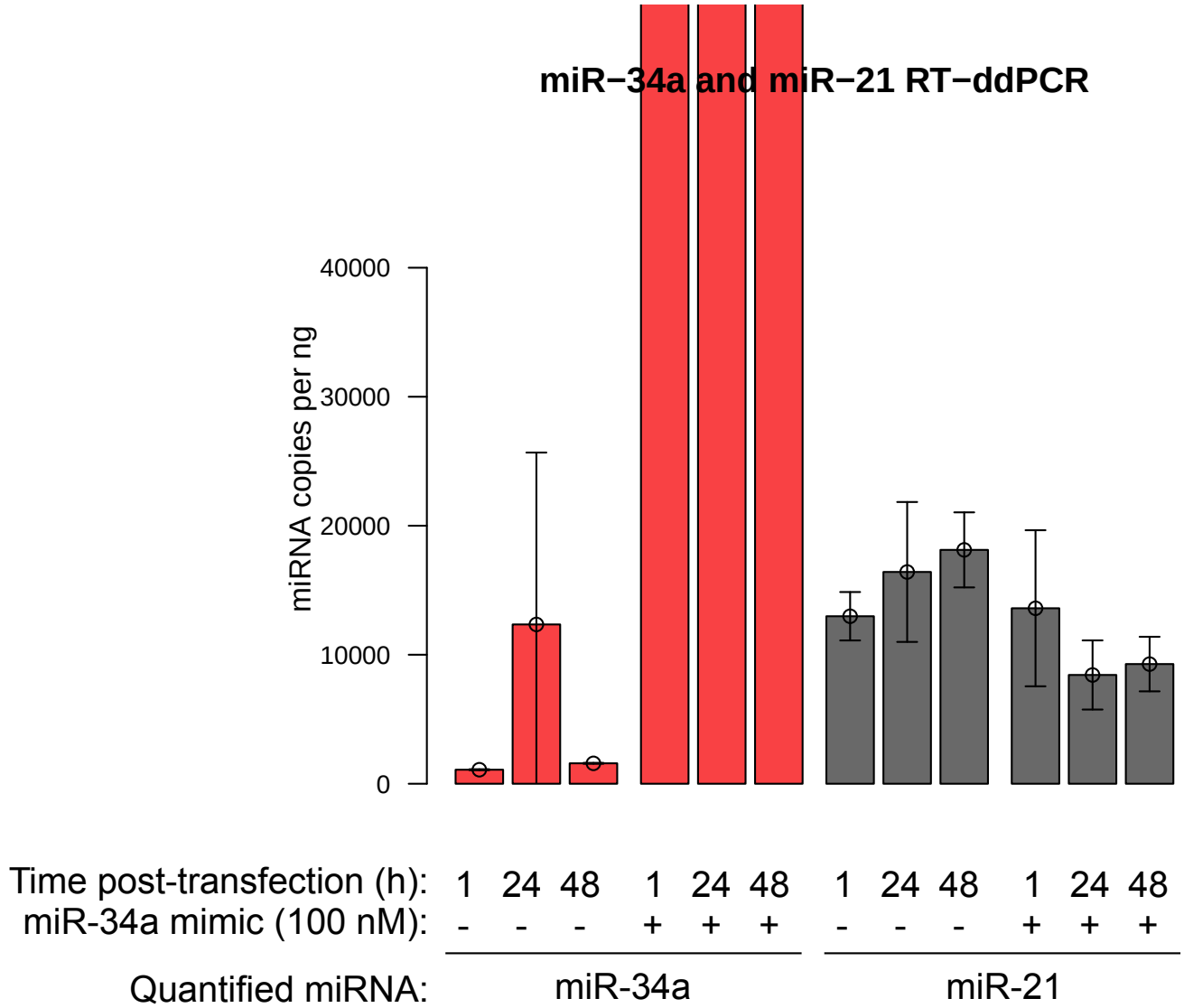

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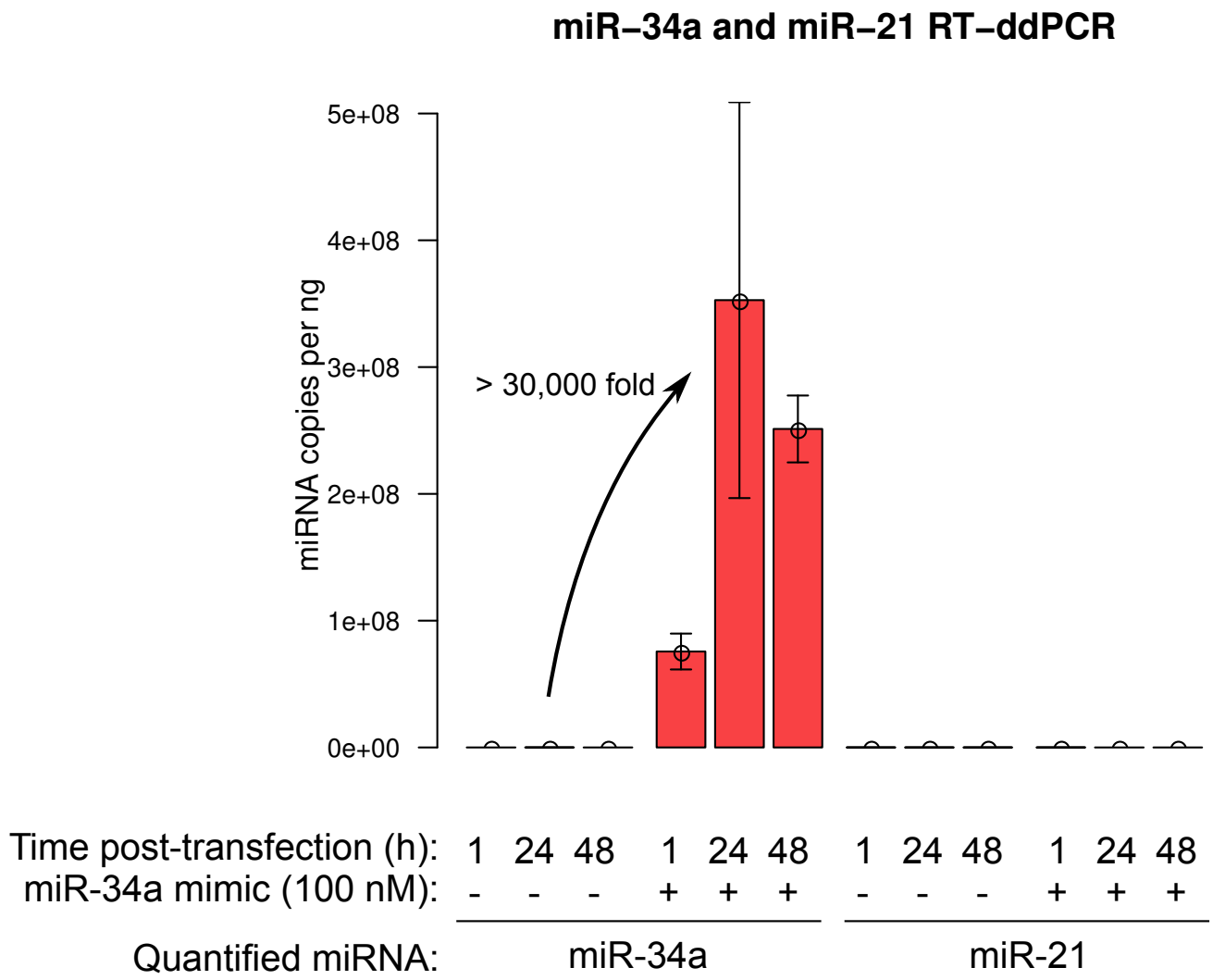

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The observed anti-proliferative effect was artifactual (due to unrealistic over-expression).

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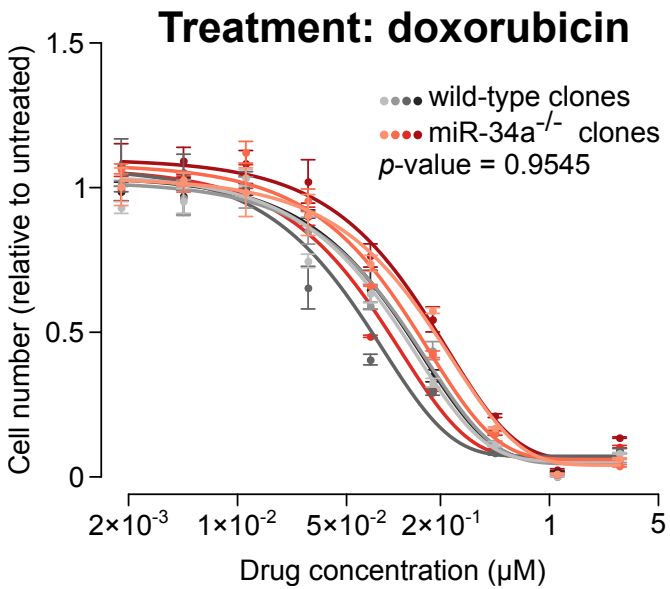

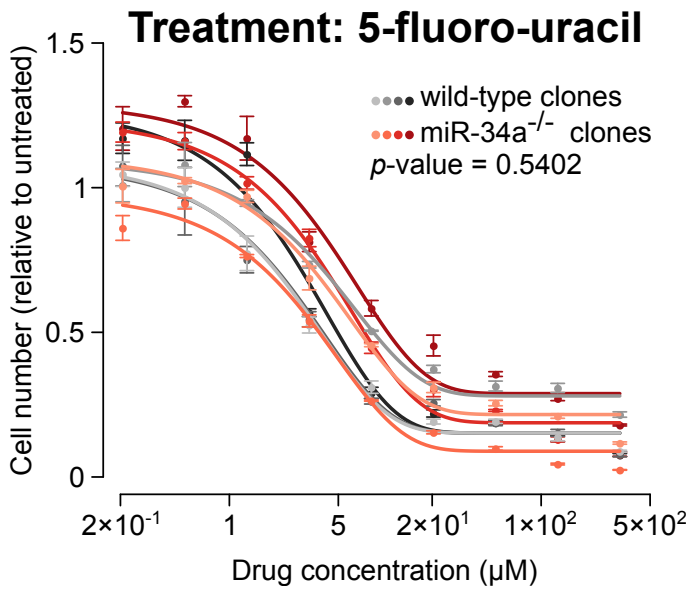

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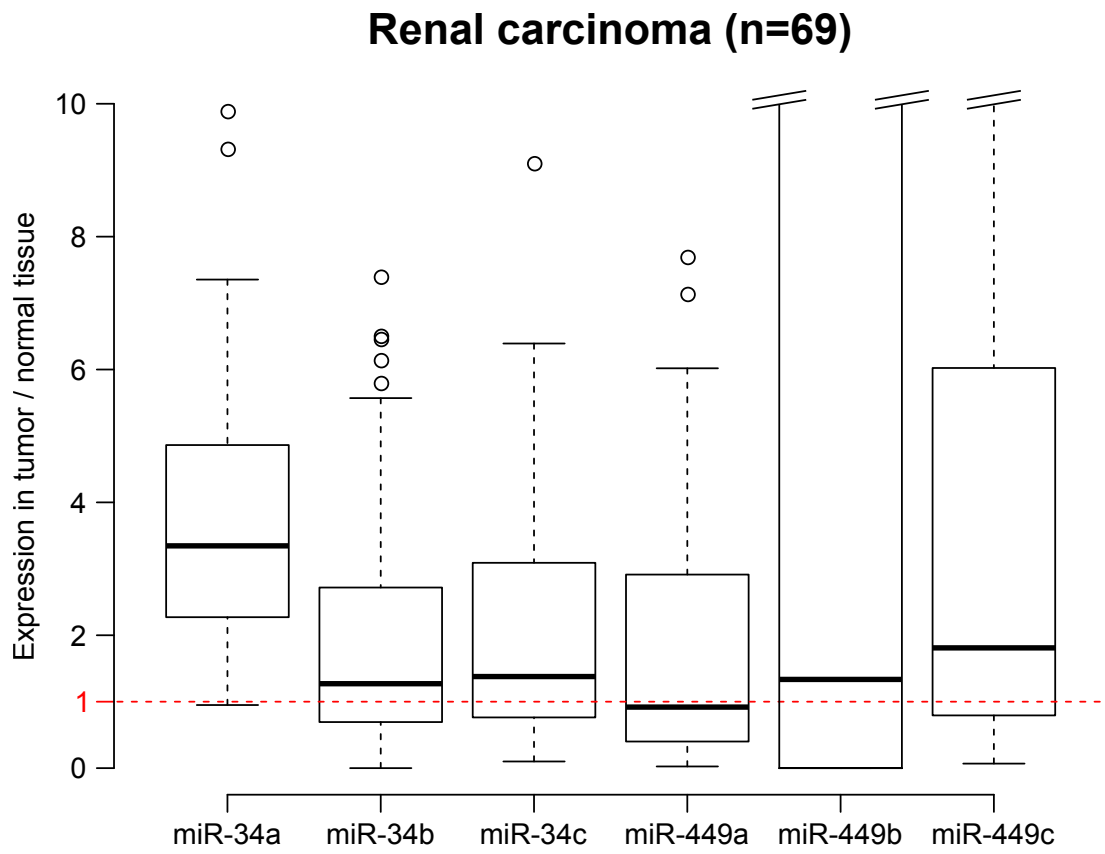

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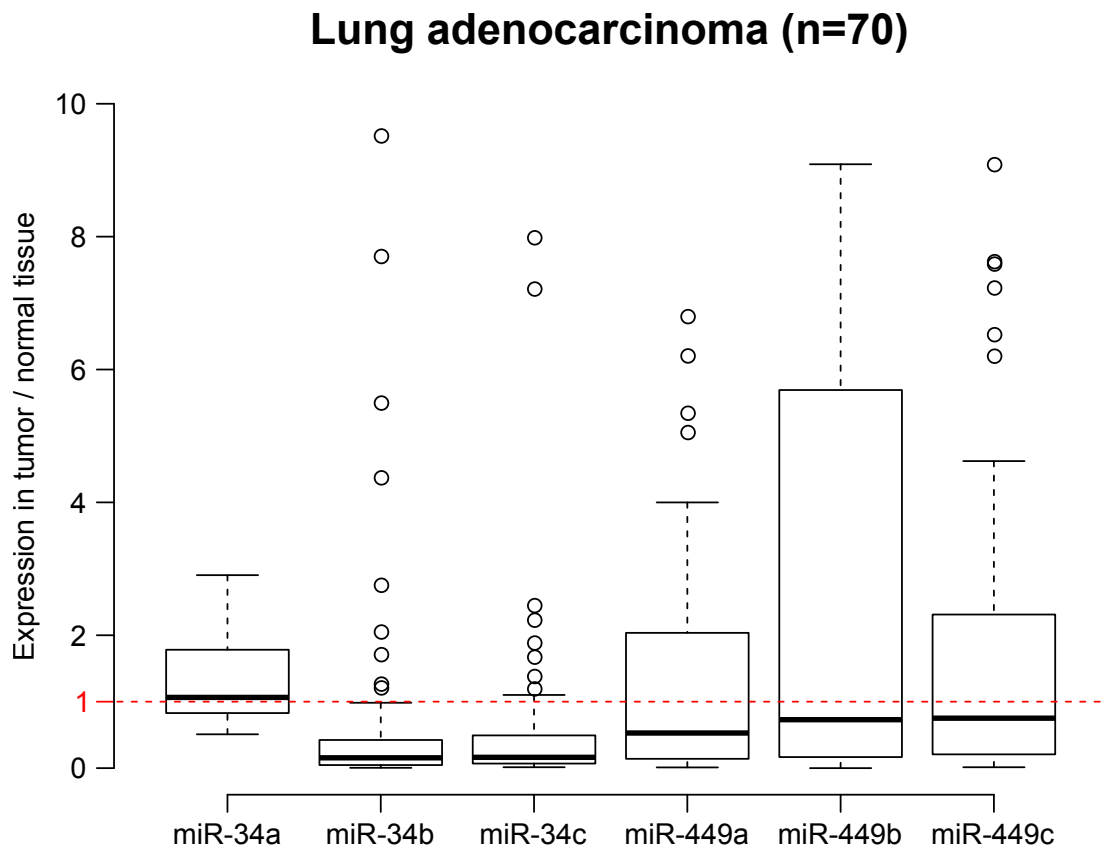

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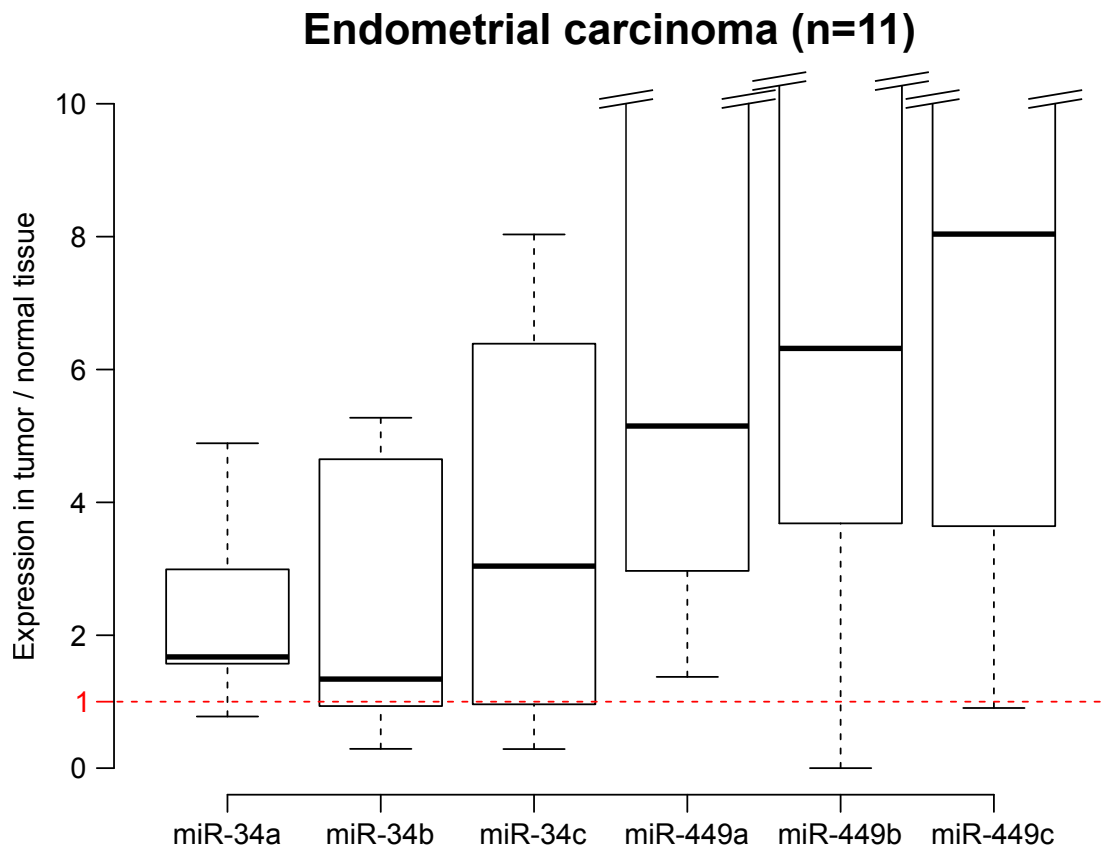

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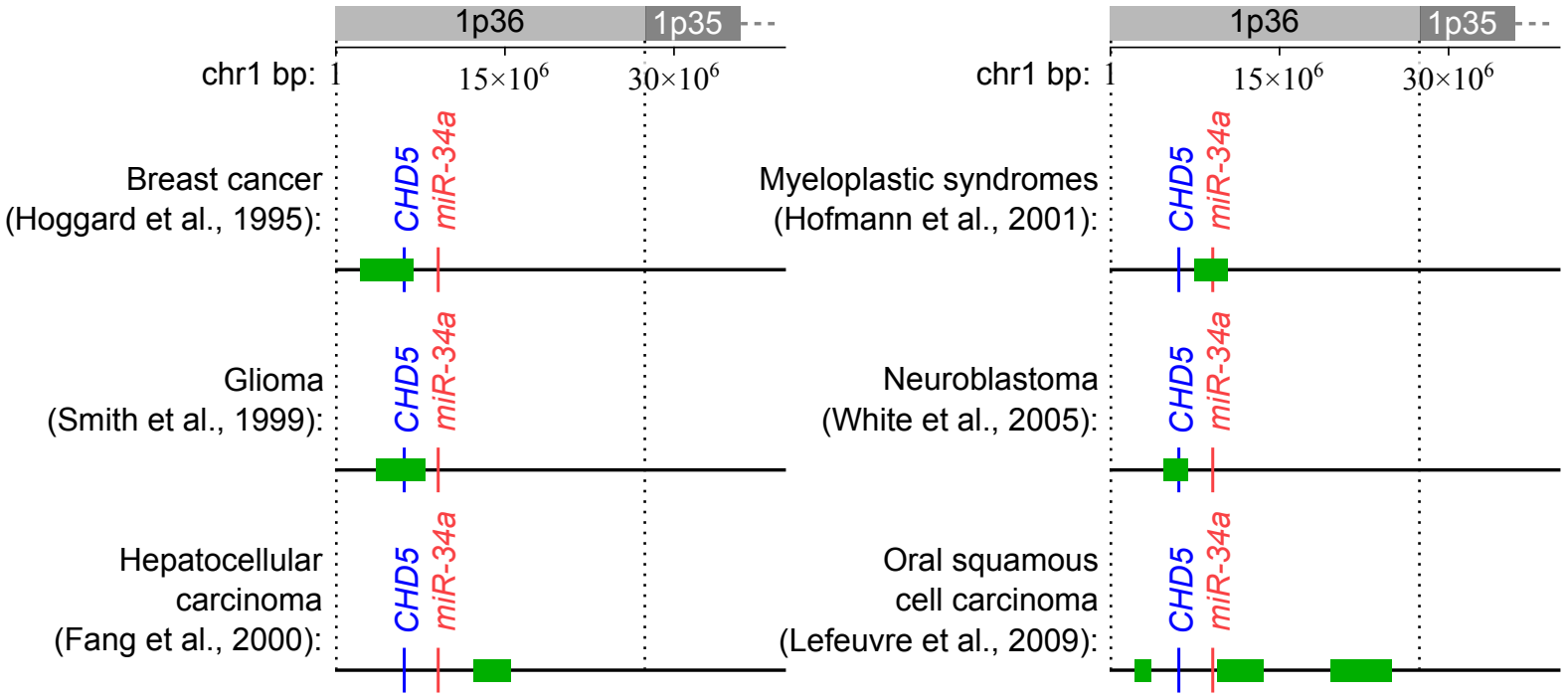

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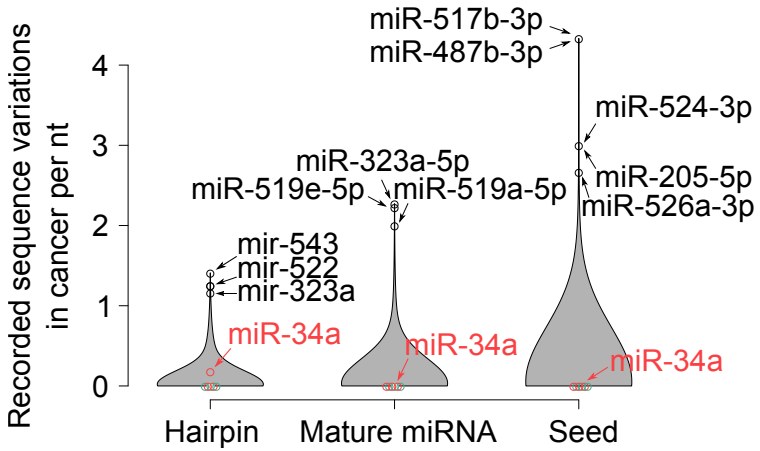

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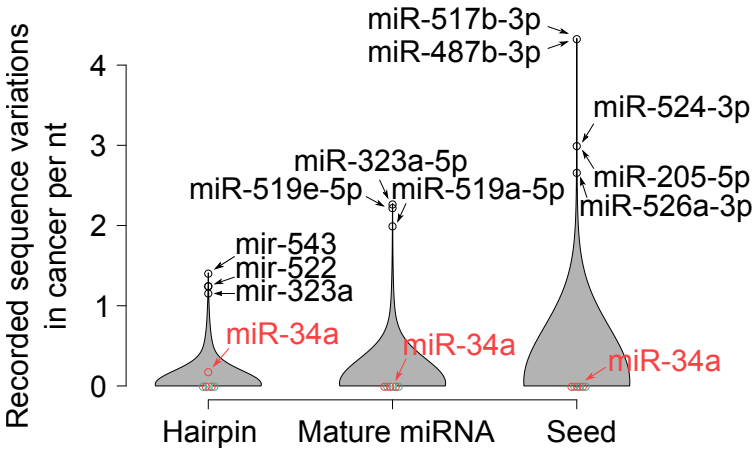

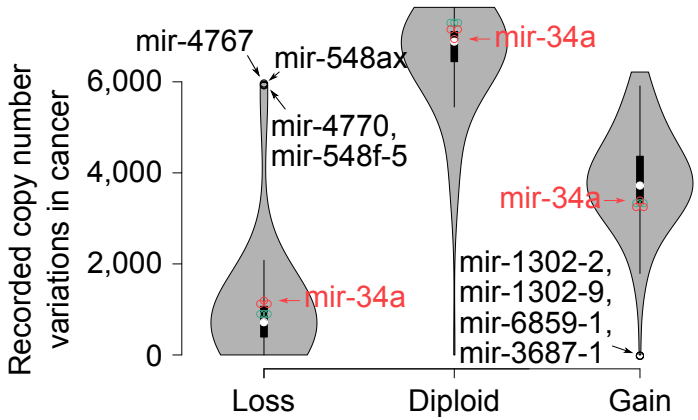

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miR-34a mutation is not a driver for 1p36 deletion in cancer.

Large amounts of transfected miR-34 is cytotoxic: why not using it to block tumor growth, no matter how un-natural it is? No better than current chemotherapy protocols (adverse effects).

Acknowledgements

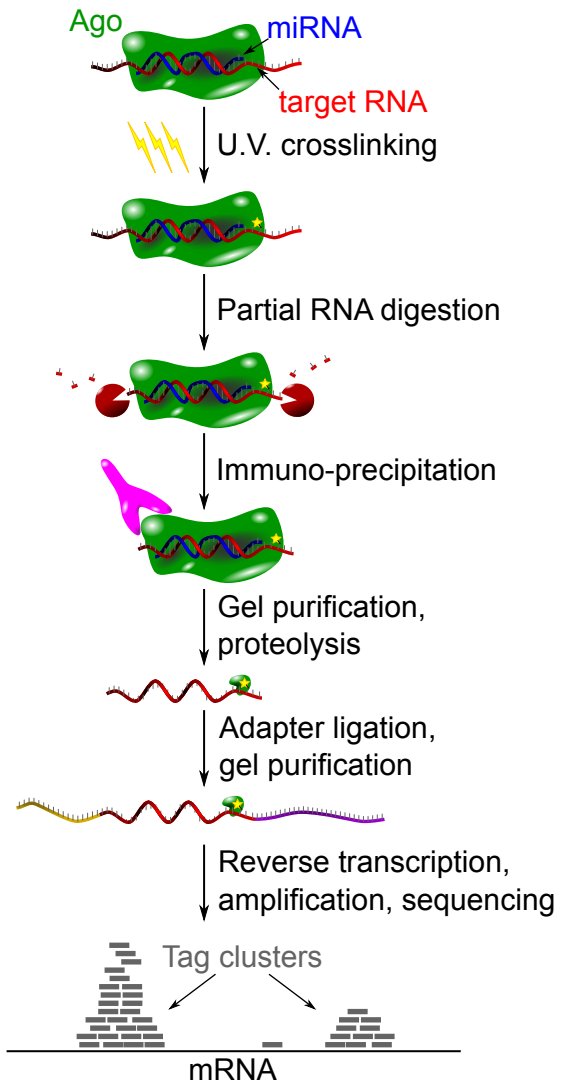
Sophie Mockly

Élisabeth Houbron

Supplementary data

- CLIP protocol
- References: p53 controls miR-34a, b and c
- miR-34 family expression in human cell lines, tissues, body fluids and murine tissues

CLIP protocol



Return

p53 controls miR-34a, b and c

- He, L. *et al.* *Nature* 447, 1130–1134 (2007).
- Bommer, G. T. *et al.* Curr Biol 17, 1298–1307 (2007).
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- Tazawa, H., *et al.* Proc Natl Acad Sci USA 104, 15472–15477 (2007).
- Raver-Shapira, N. *et al.* Mol Cell 26, 731–743 (2007).

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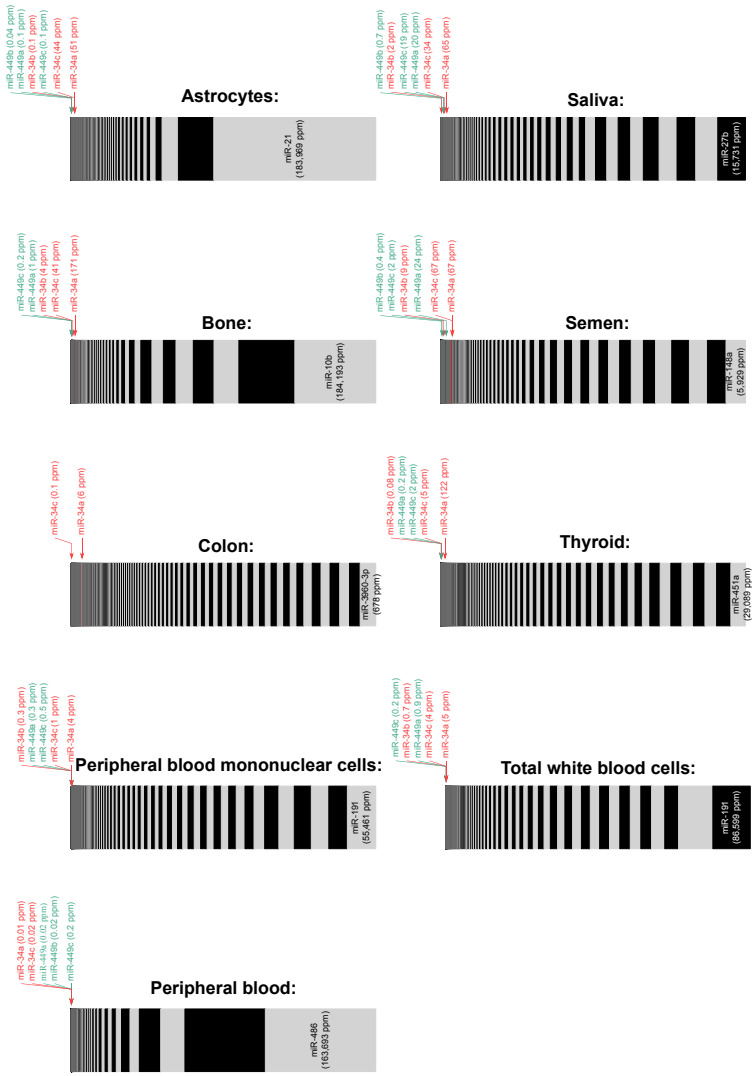

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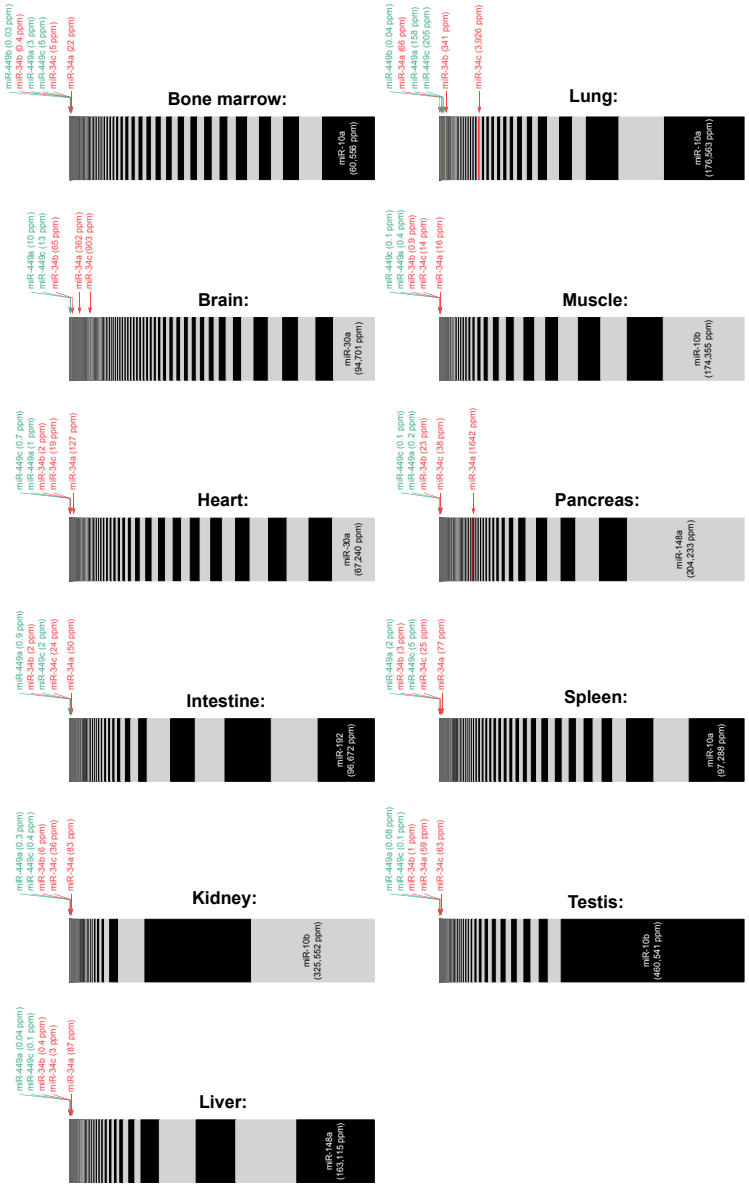

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