

A rationalized definition of tumor suppressor microRNAs excludes miR-34a

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<http://www.igh.cnrs.fr/equip/Seitz/GS021.pdf>

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miR-34a, a
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A fuzzy definition for tumor suppressor miRNAs

Tumor suppressors: selectively lost in cancers;
anti-proliferative action under their endogenous expression
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microRNAs (“miRNAs”): regulatory RNAs, guiding their effector proteins to specific targets.

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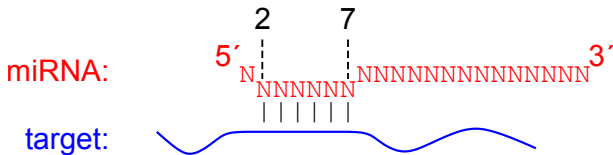
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- ▶ both criteria ([Adams et al., 2016](#)).

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No reason to restrict the initial definition to coding genes.

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The most heavily studied candidate tumor suppressor miRNA:

- ▶ 6 miRNAs in the family:

Human miR-34 family members:

miR-34b-5p	AGGCAGUGU --CAUUAGCUGAUUG--
miR-34c-5p	AGGCAGUGU --AGUUAGCUGAUUGC
miR-34a-5p	UGGCAGUGU --C-UUAGCUGGUUGU
miR-449a	UGGCAGUGU AUUGUUAGCUGGU---
miR-449b-5p	AGGCAGUGU AUUGUUAGCUGGC---
miR-449c-5p	AGGCAGUGU AUUGC <u>UAGC</u> -GGCUGU

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Seed

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Failure of the trial ([Beg et al., 2017](#); [Hong et al., 2020](#)).
Mixed results in mouse (encouraging results in pre-clinical assays; but the *miR-34a*^{-/-}, *miR-34b*^{-/-}, *miR-34c*^{-/-} triple KO does not exhibit abnormal p53 response: [Concepcion et al., 2012](#)).

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Comparison of miRNA expression in primary tumor and normal adjacent tissue ([GDC data portal](#)).

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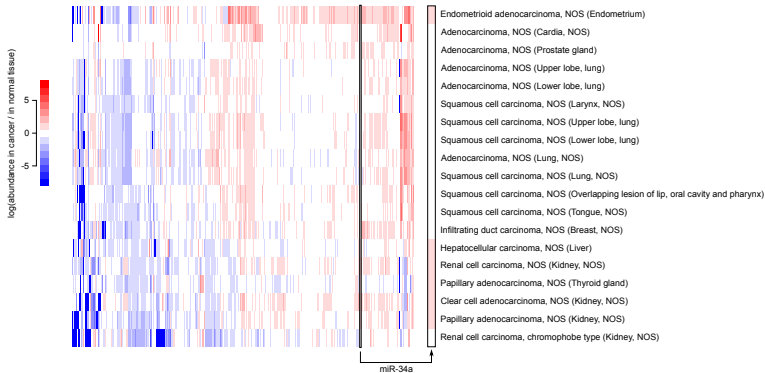
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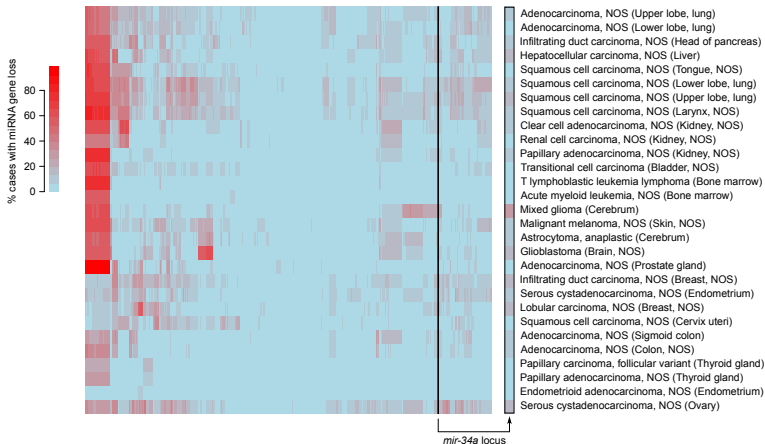
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Comparison of miRNA gene loss in cancer (GDC data portal):



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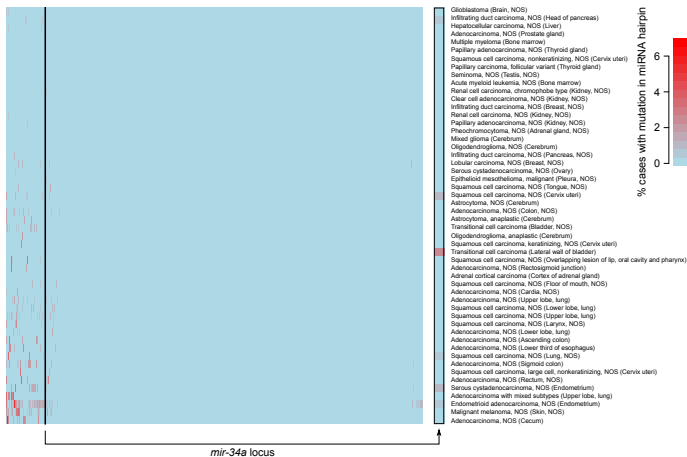
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Comparison of miRNA sequence variation in cancer (GDC data portal):



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Available data: over-expression experiments.

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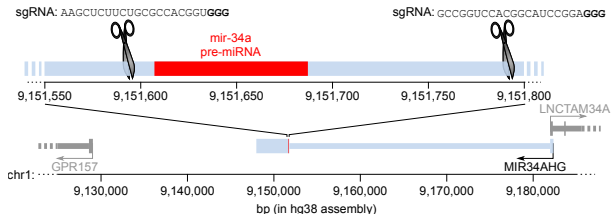
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In human HCT-116 and HAP1 cells:



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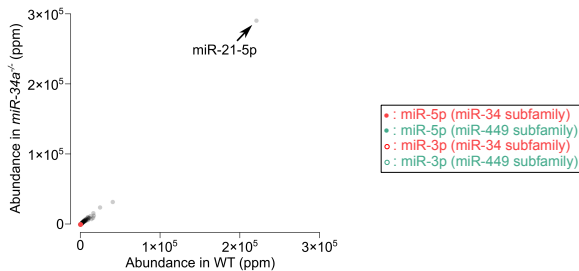
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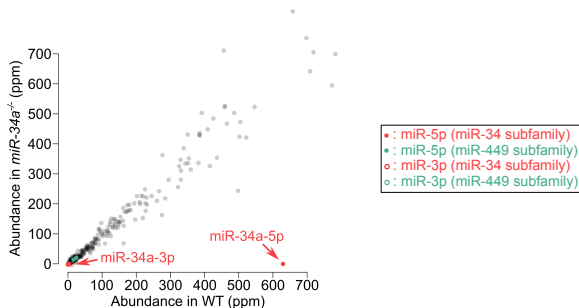
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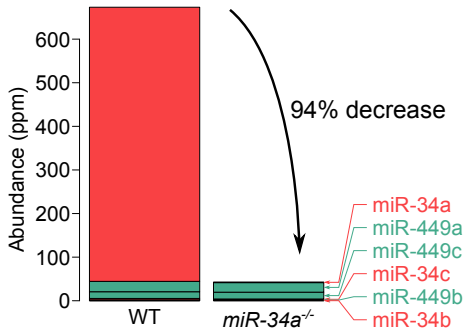
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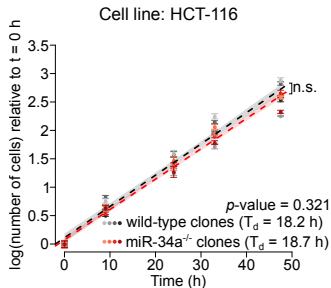
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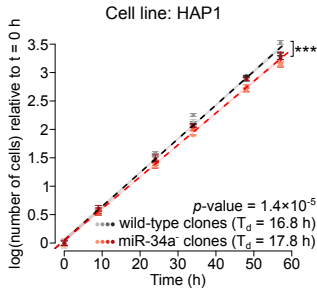
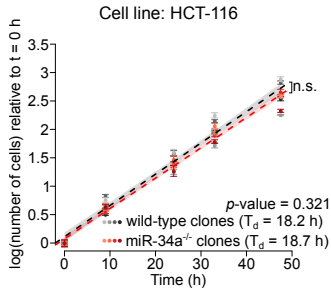
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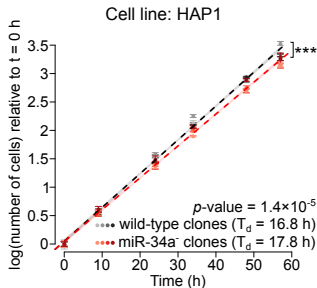
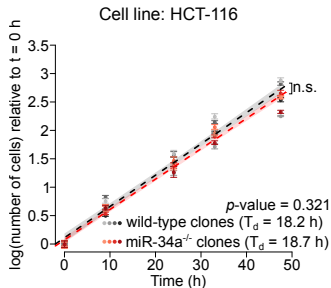
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→ Proliferation arrest may be an artifact of miR-34a overexpression.

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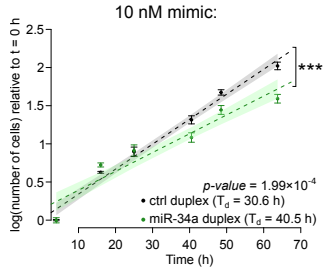
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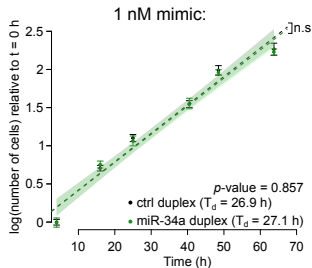
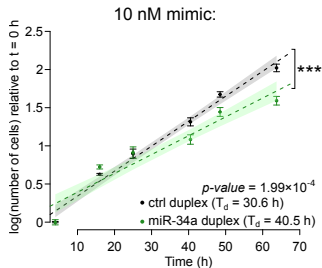
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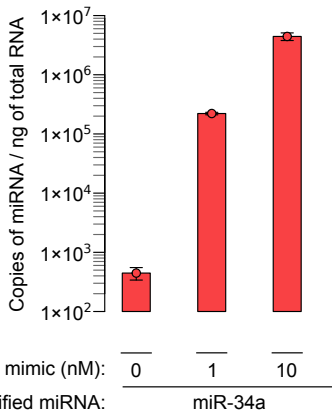
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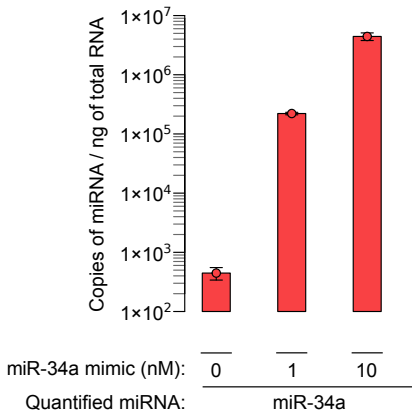
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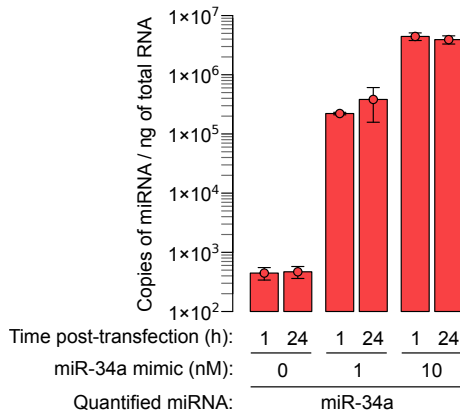
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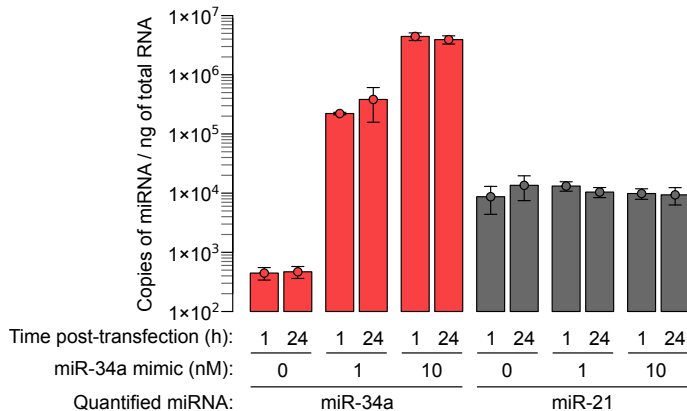
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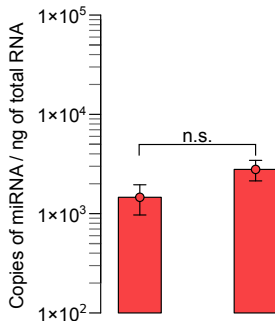
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Time post-treatment (h):

24

24

Doxorubicin treatment:

-

+

Quantified miRNA:

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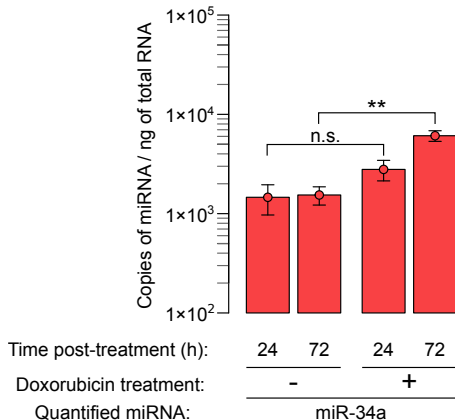
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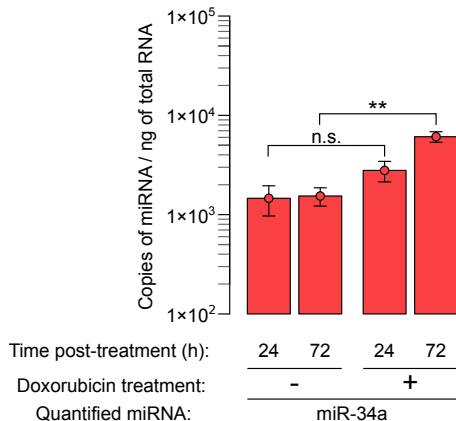
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72 h doxorubicin at IC_{50} (7×10^{-8} M) over-expresses miR-34a by 4.7-fold.

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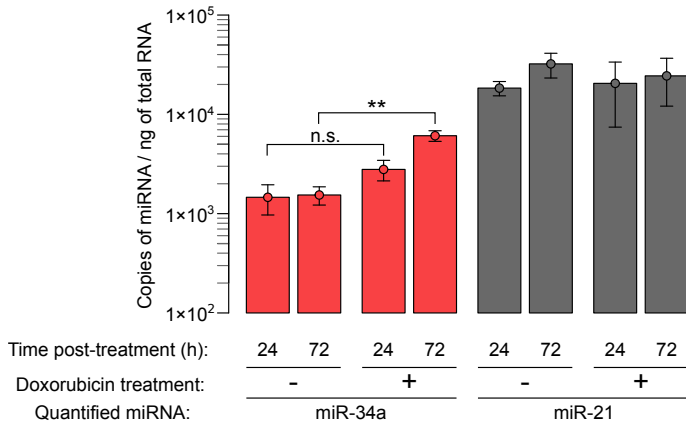
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72 h doxorubicin at IC₅₀ (7×10^{-8} M) over-expresses miR-34a by 4.7-fold.

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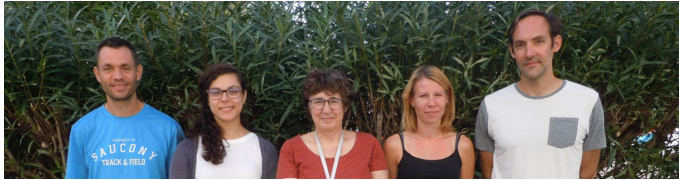
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Sophie
Mockly

Élisabeth
Houbron

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- ▶ References: p53 controls miR-34a, b and c
- ▶ Minimal regions of consistent deletions in cancer
- ▶ No effect of miR-34a against genotoxic stress
- ▶ miR-34 family expression in human cell lines, tissues, body fluids and murine tissues

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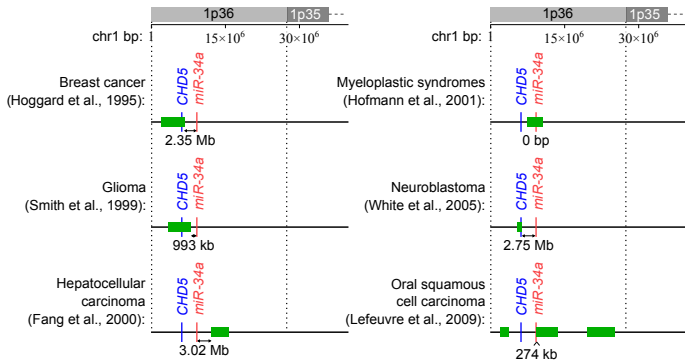
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Hoggard *et al.*, 1995; Smith *et al.*, 1999; Fang *et al.*, 2000; Hofmann *et al.*, 2001; White *et al.*, 2005; Lefevre *et al.*, 2008.

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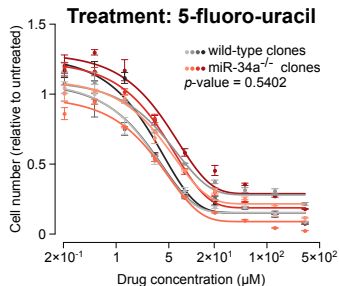
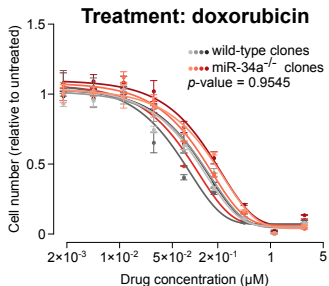
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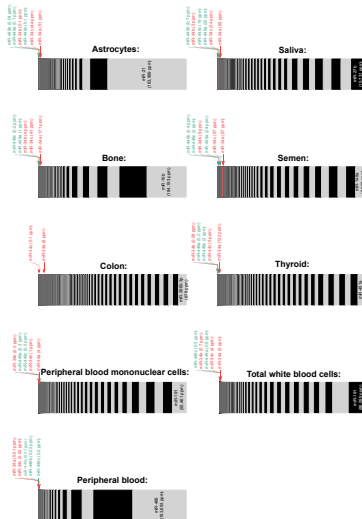
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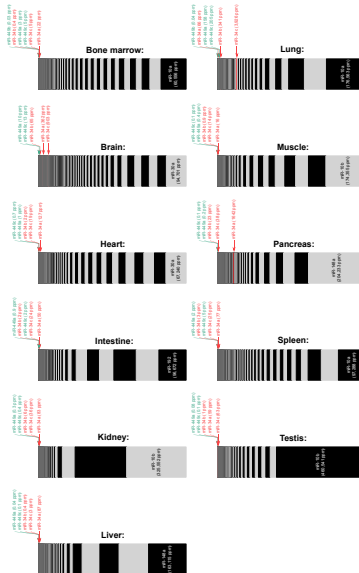
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