

Revisiting the status of tumor suppressor microRNAs: the case of miR-34a

Hervé Seitz

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<http://www.igh.cnrs.fr/equip/Seitz/CRCT23.pdf>

miRNAs and their targets

Tumor suppressor
microRNAs: the
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Fuzzy definition for
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miR-34a, a
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miR-34a is not
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miR-34a is not a
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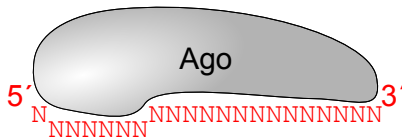
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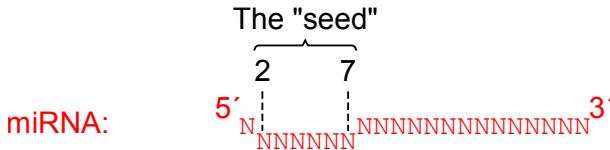
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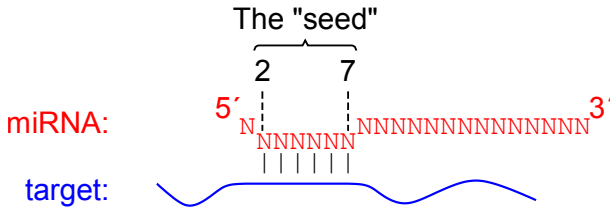
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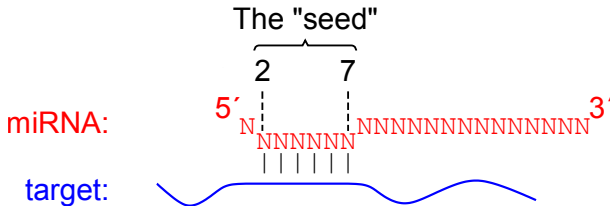
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Most efficient binding sites:

- ▶ in 3' UTRs
- ▶ supplemented by match to nt 8 or A facing nt 1
- ▶ in a favorable sequence context

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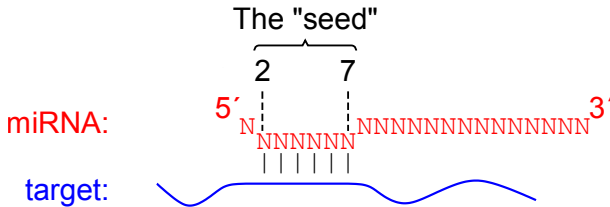
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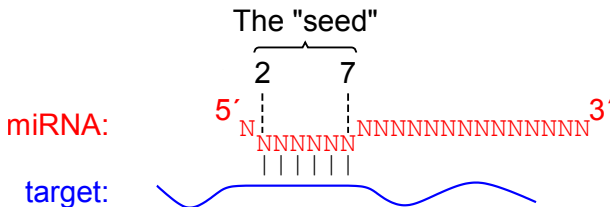
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→ Computational target prediction.

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- ▶ miRNAs are easy to quantify

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- ▶ miRNAs are easy to quantify
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—→ Many studies describing differential miRNA abundance in cancer vs. normal tissue

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- ▶ miRNAs are easy to quantify
- ▶ their targets are easy to **predict**

—→ Many studies describing differential miRNA abundance in cancer vs. normal tissue, then proposing a causal role for miRNAs based on automatic annotation of their predicted targets.

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- ▶ miRNAs are easy to quantify
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—→ Many studies describing differential miRNA abundance in cancer vs. normal tissue, then proposing a causal role for miRNAs based on automatic annotation of their predicted targets.

These targets are mere predictions; enrichment in an annotated function is no proof of a biological effect.

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Tumor suppressors: selectively lost in cancers;
anti-proliferative action under their endogenous expression
level ([Weinberg, 1991](#)).

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Explicitly excludes genes with cytotoxic or cytostatic activity
only upon unrealistic overexpression.

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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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miR-34a, a candidate tumor suppressor

The most heavily studied candidate tumor suppressor miRNA:

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- ▶ 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>CUAGC</u> -GGCUGU

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—> Over the last 14 years: a myriad of studies; a clinical trial (“MRX34”: a synthetic miR-34a, administered to patients with solid tumors).

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Failure of the trial ([Beg et al., 2017](#); [Hong et al., 2020](#)).

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→ Over the last 14 years: a myriad of studies; a clinical trial (“MRX34”: a synthetic miR-34a, administered to patients with solid tumors).

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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Following analyses: published in [Mockly *et al.*, 2022.](#)

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

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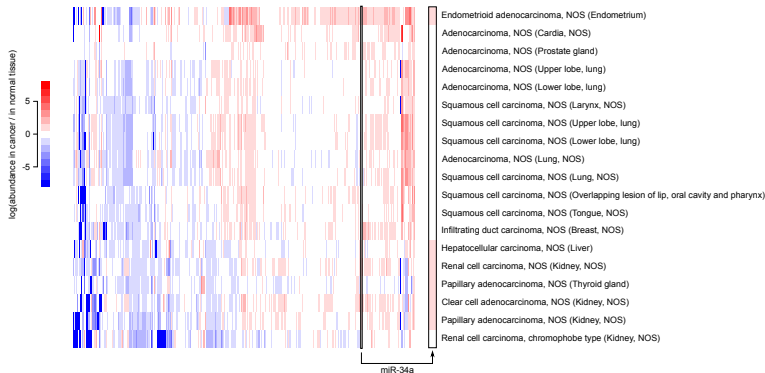
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(cancer types with ≥ 10 analyzed cases)

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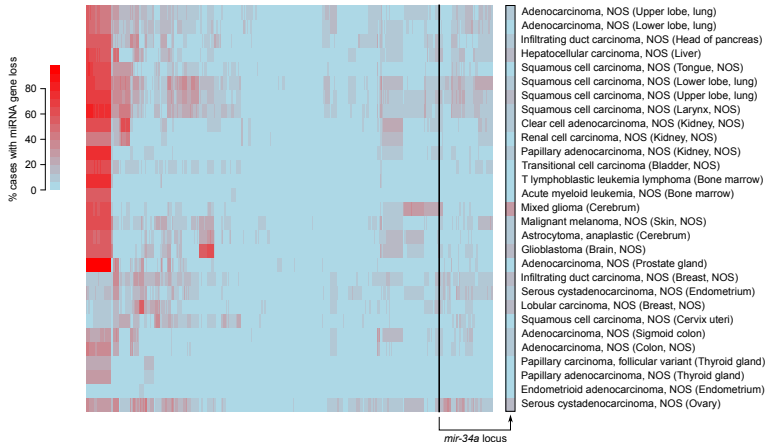
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Comparison of miRNA gene loss in cancer (GDC data
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(cancer types with ≥ 100 analyzed cases)

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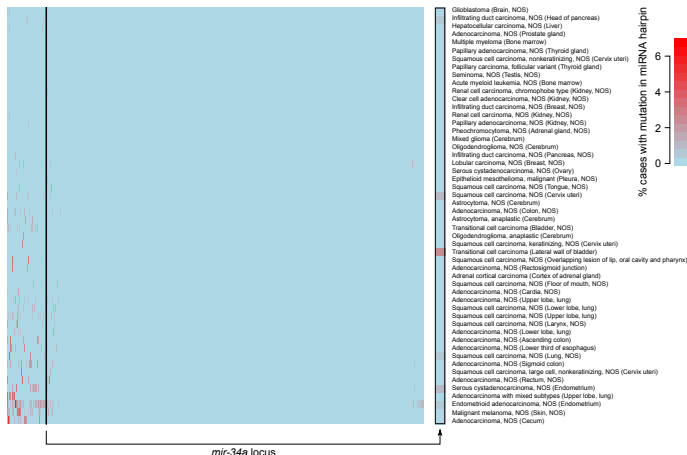
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Comparison of miRNA sequence variation in cancer (GDC data portal):



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Available data: over-expression experiments.

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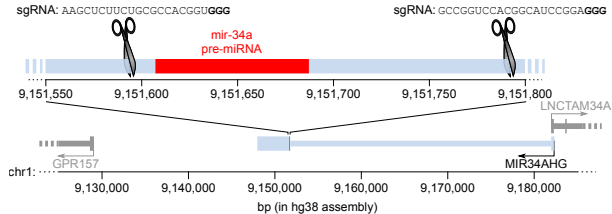
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In human HCT-116 and HAP1 cells:



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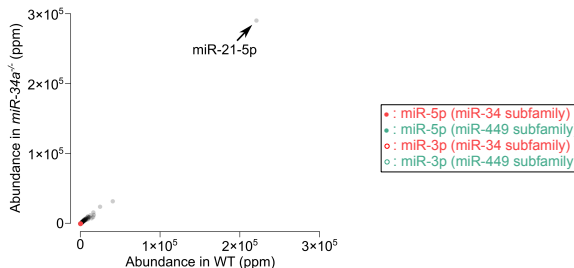
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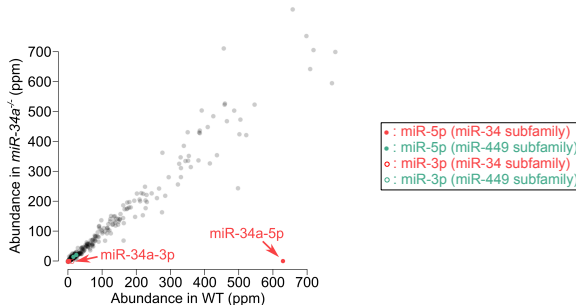
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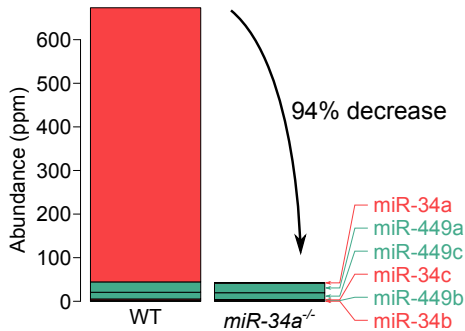
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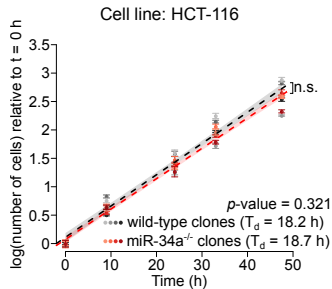
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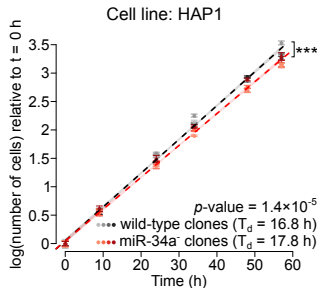
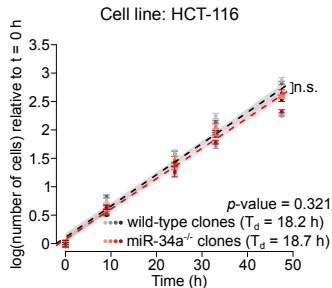
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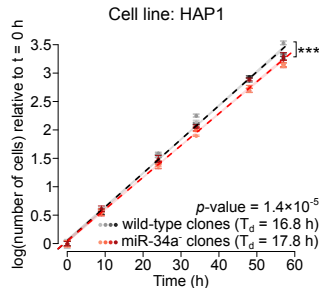
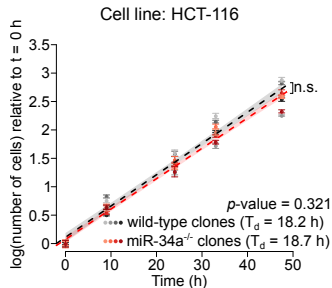
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→ Proliferation arrest may be an artifact of miR-34a overexpression.

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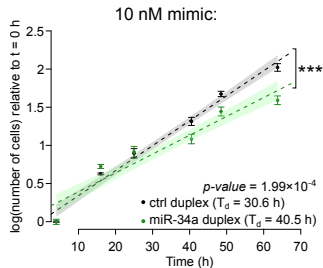
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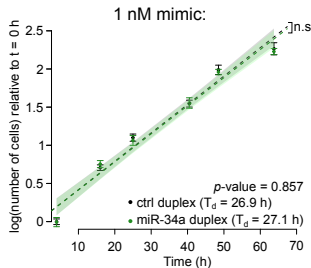
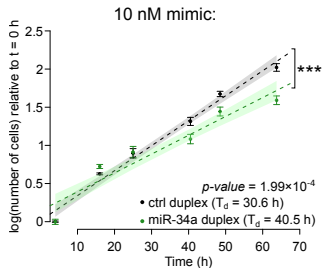
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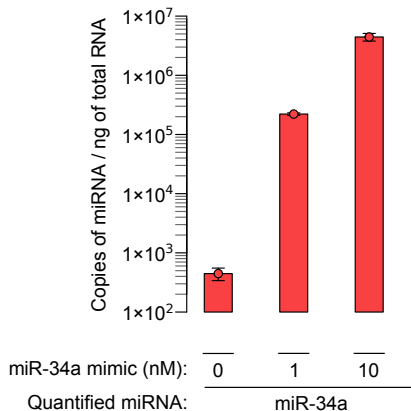
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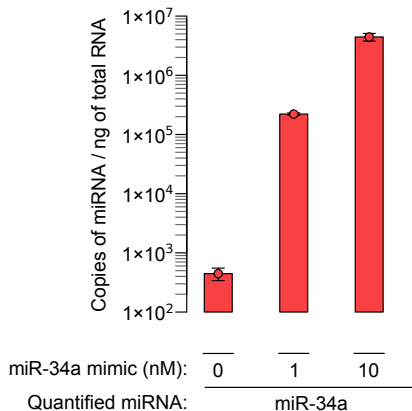
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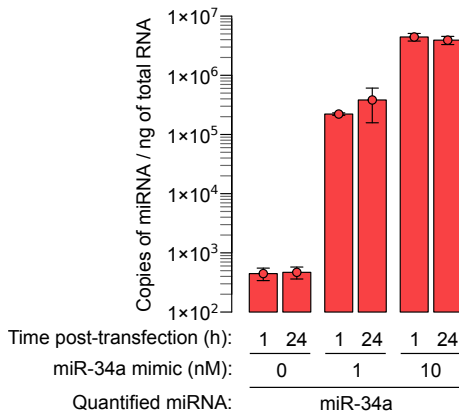
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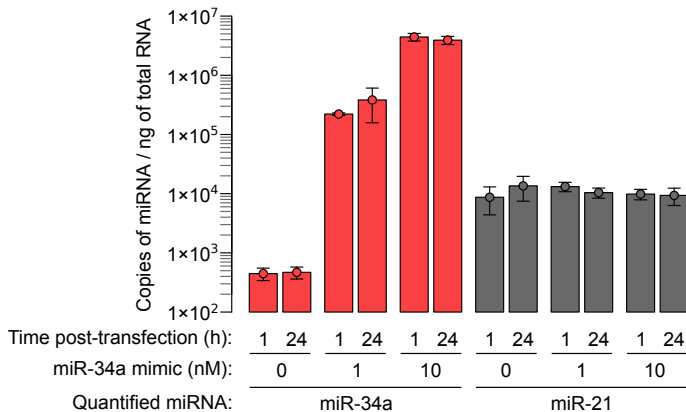
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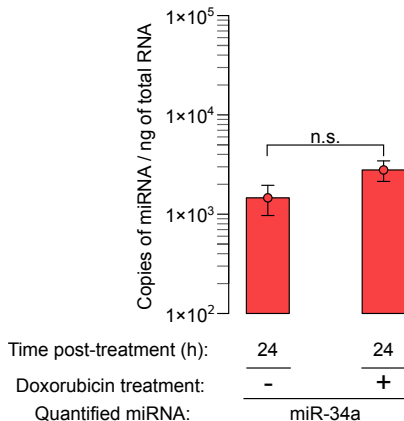
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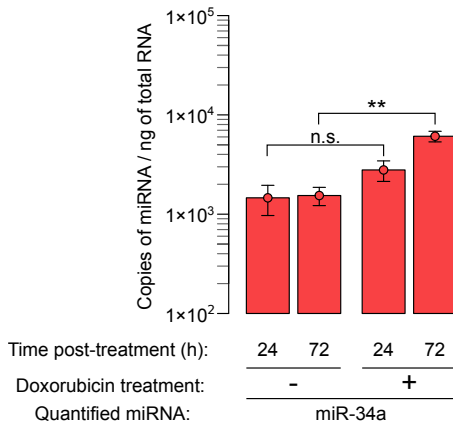
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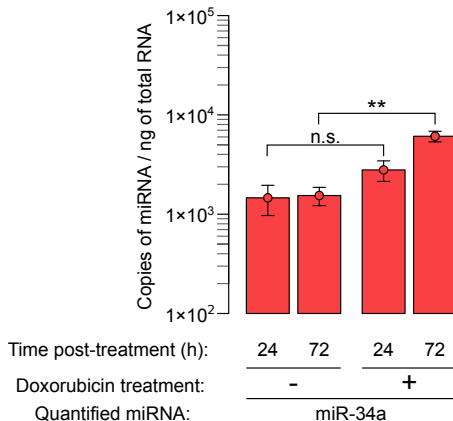
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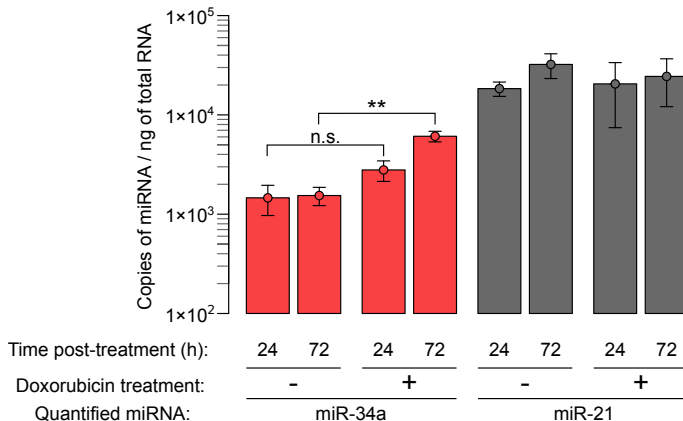
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Large amounts of transfected miR-34 is cytotoxic: why not using it to block tumor growth, no matter how un-natural it is? No better than current chemotherapy protocols (adverse effects).

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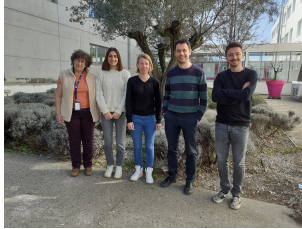
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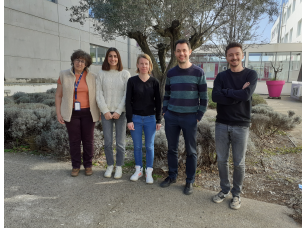
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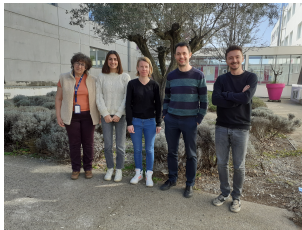
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- ▶ miRNA abundances in human cell lines
- ▶ miRNA abundances in human tissues and body fluids
- ▶ miRNA abundances in murine tissues

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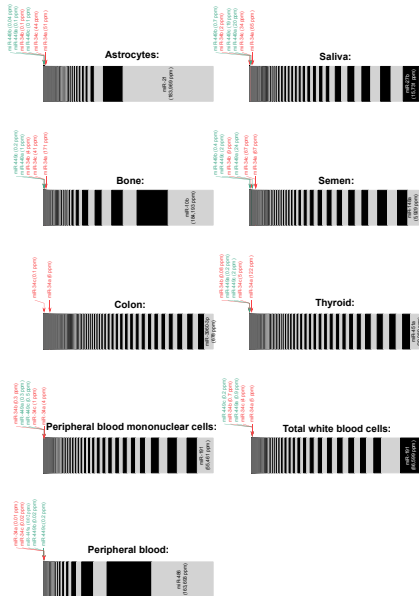
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