XVIII IWCLL

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Leukemia specific delivery of miR-29b induces epigenetic reprogramming with cell cycle arrest and therapeutic benefit in CLL

Poster #2188

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Disclosures

- None

miR-29b in CLL

- MiR-29b functions as a tumor suppressor.
- Aggressive CLL is characterized by **miR-29b** downregulation.
- Higher miR-29b expression is associated with better outcome.

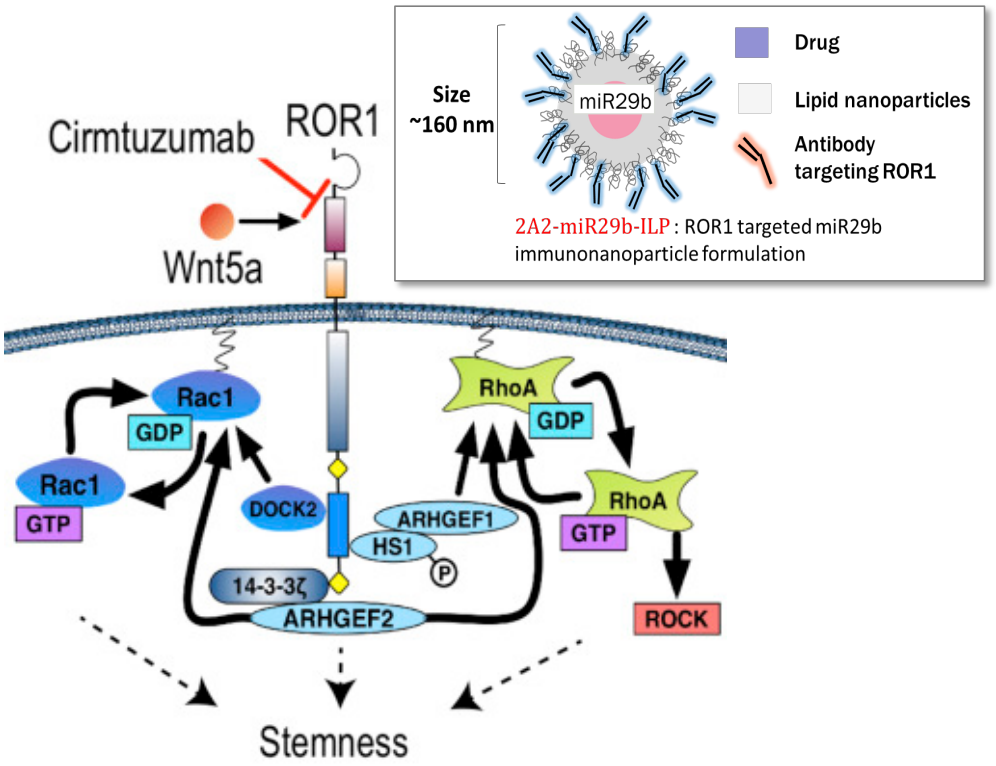
We hypothesize that over expression of miR29b in CLL cells will have therapeutic benefit.

Need for selective targeting of miR29b in CLL

- miR29b is expected to have off target effects in CLL.
- Pleotropic effects of miR29b in tissue homeostasis pose a problem.
- Limitations associated with immune-related adverse effects imply the need for **targeted delivery** of miR-29b in CLL.
- Evaluation of miR-29b in human cell lines in immunocompromised xenograft models precludes influence of the immune compartment.

We hypothesize that leukemic B cell specific delivery of miR29b in CLL will have therapeutic benefit while sparing normal B cells.

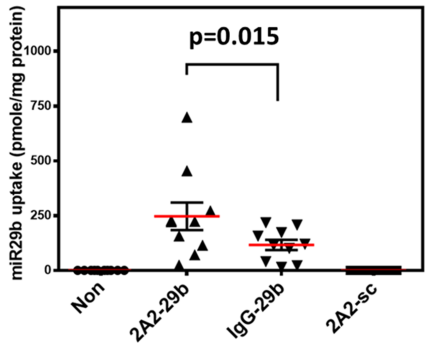
ROR1 as a target for CLL specific drug delivery



- Receptor tyrosine kinase-like orphan receptor
- tumor restricted -Unique to CLL,MCL and some ALL B cells but not normal B cells.
- Disease status does not alter expression
- Internalization property

miR-29b delivery reduces DNMTs, SP1, viability in Primary B-CLL cells

A



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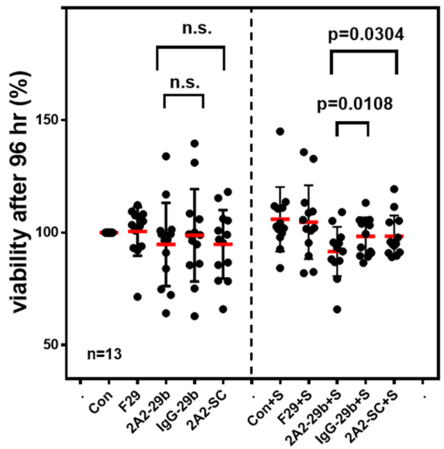

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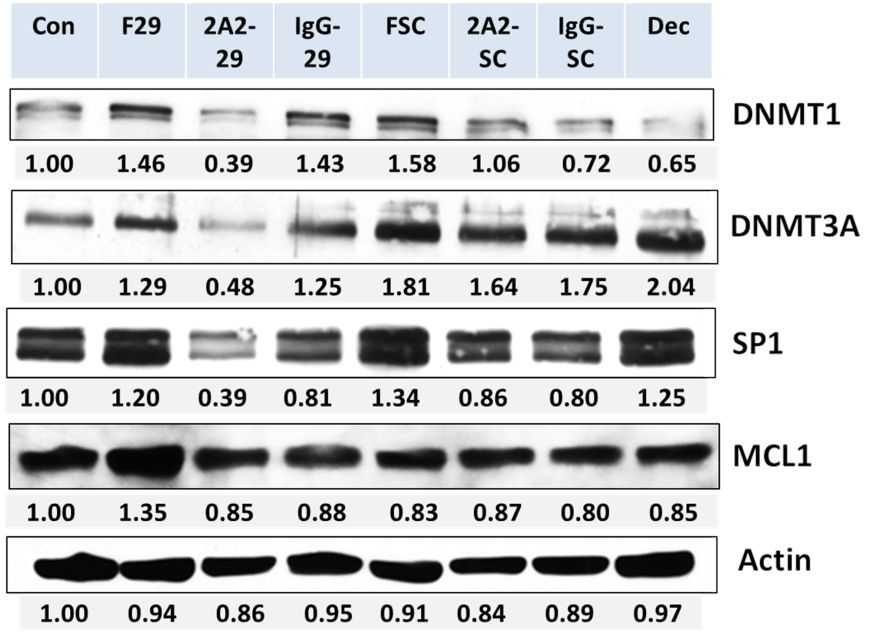
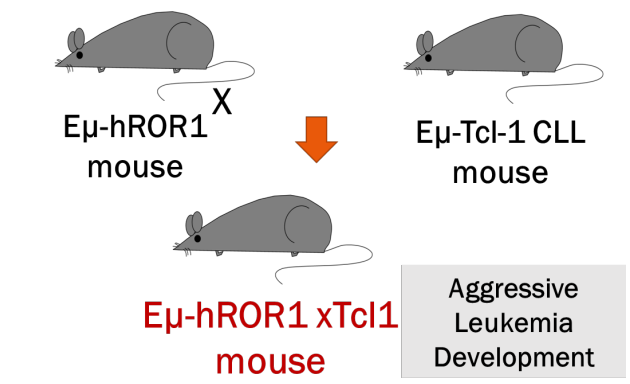
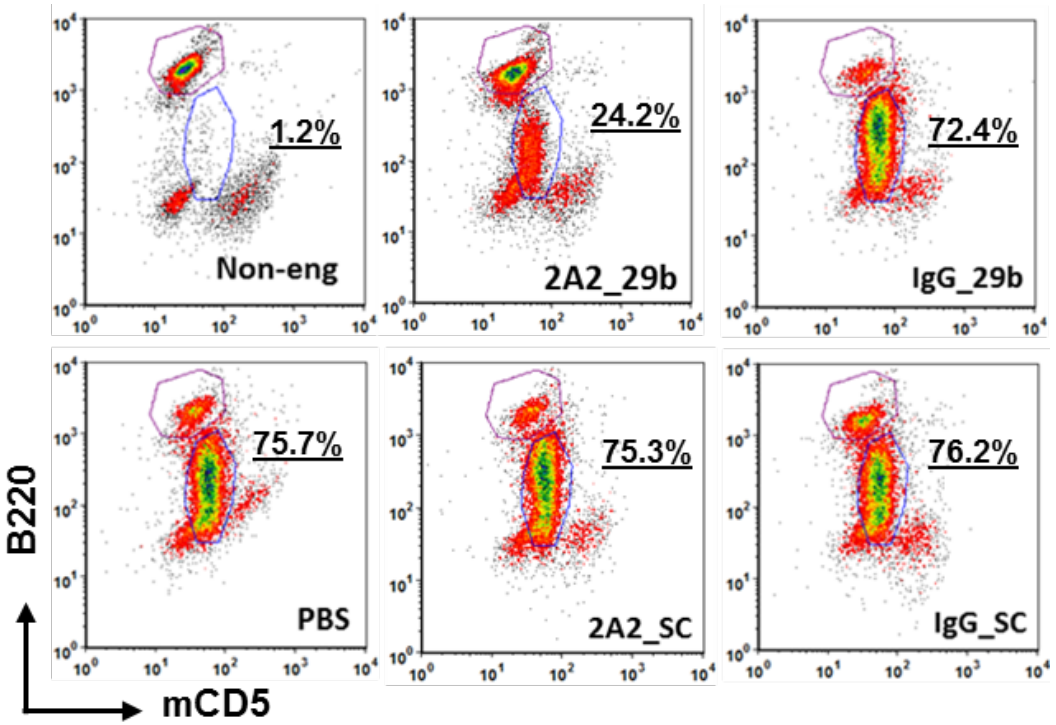


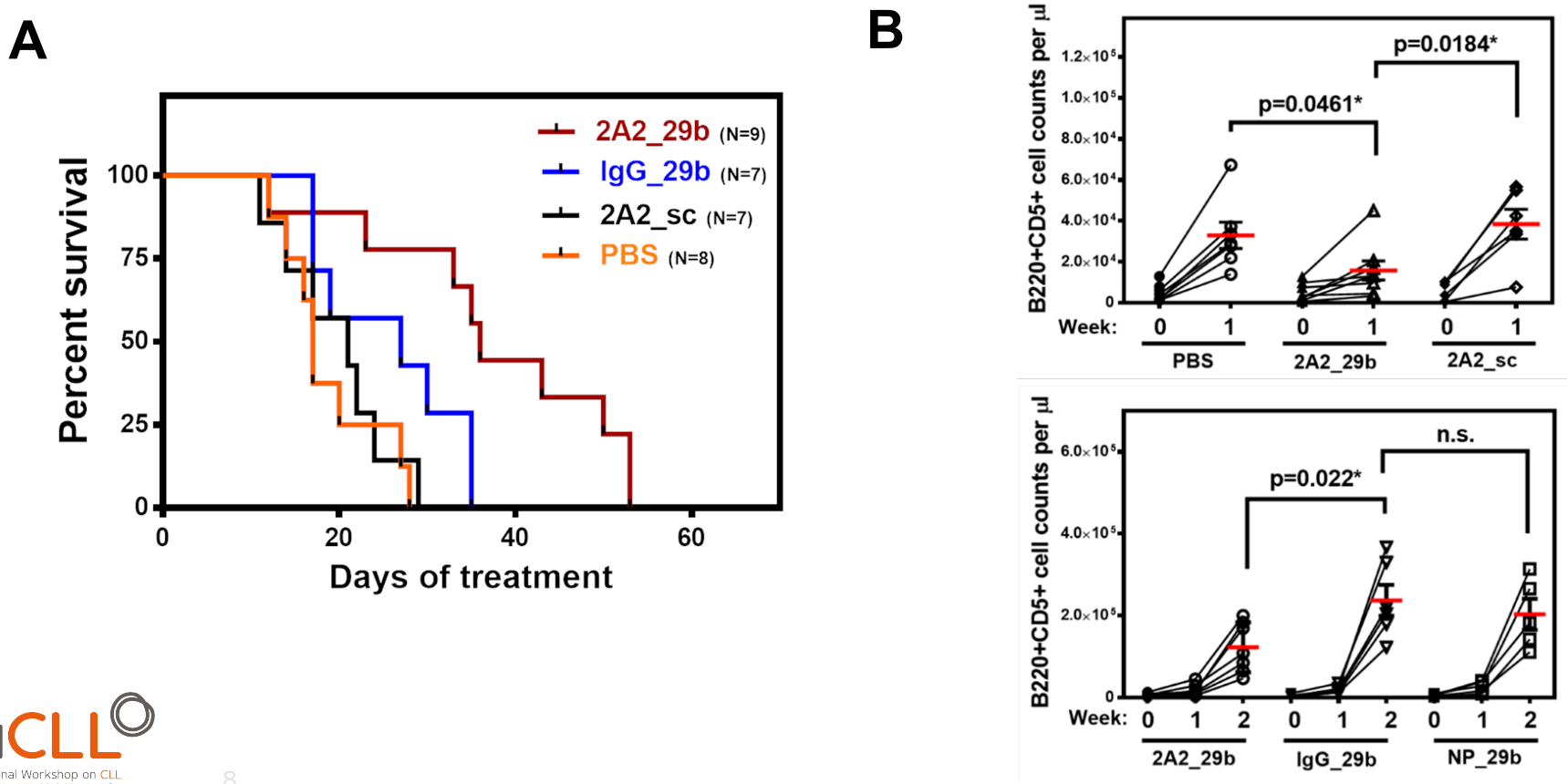
ROR1 targeted 2A2-miR29b-ILP decreases the circulating leukemic cells



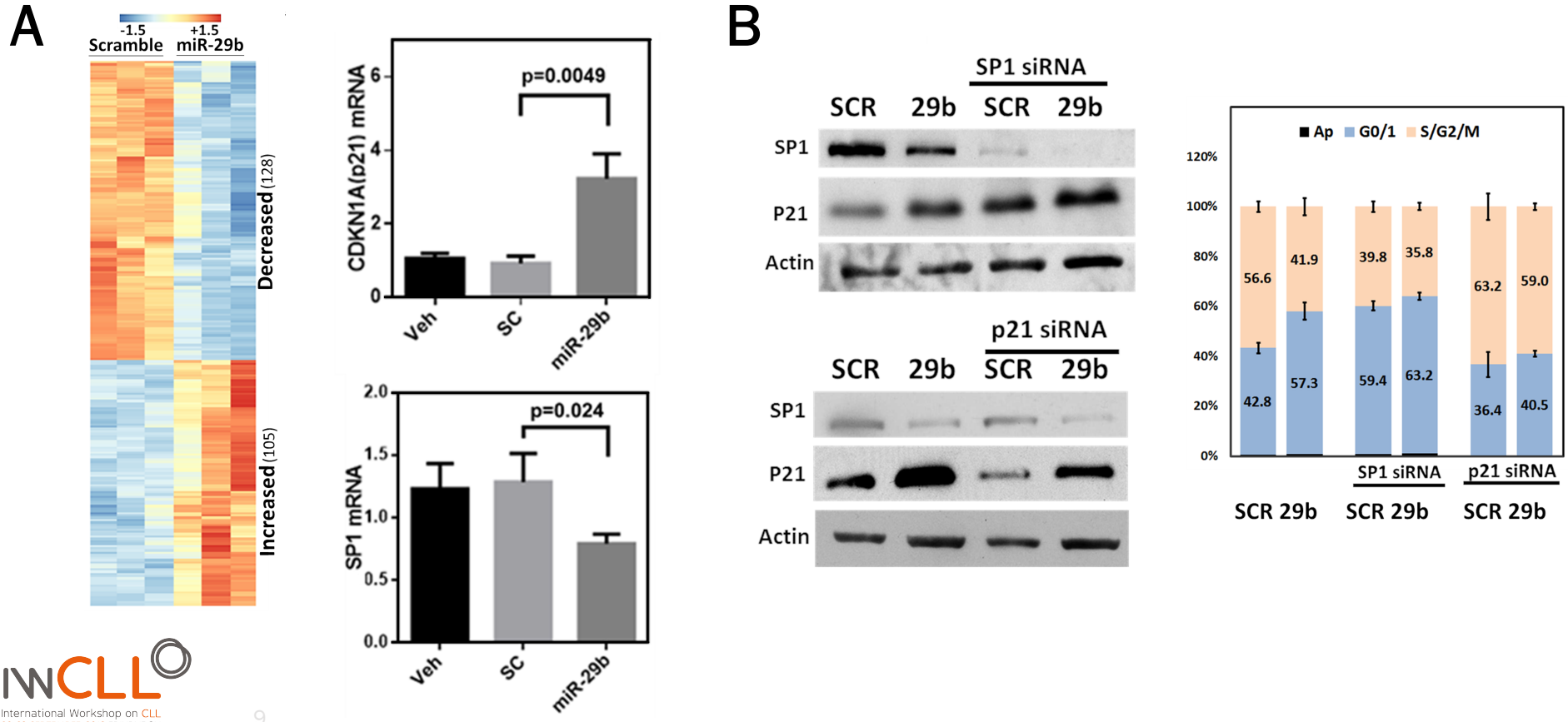


* 2 weeks post-treatment

In-vivo efficacy of ROR1-ILP-miR29b formulation

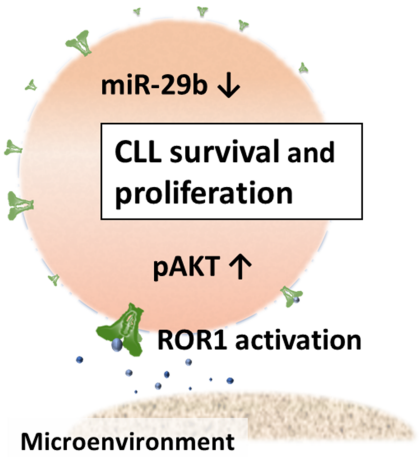


miR-29b suppressed leukemic growth in SP1/p21 dependent manner

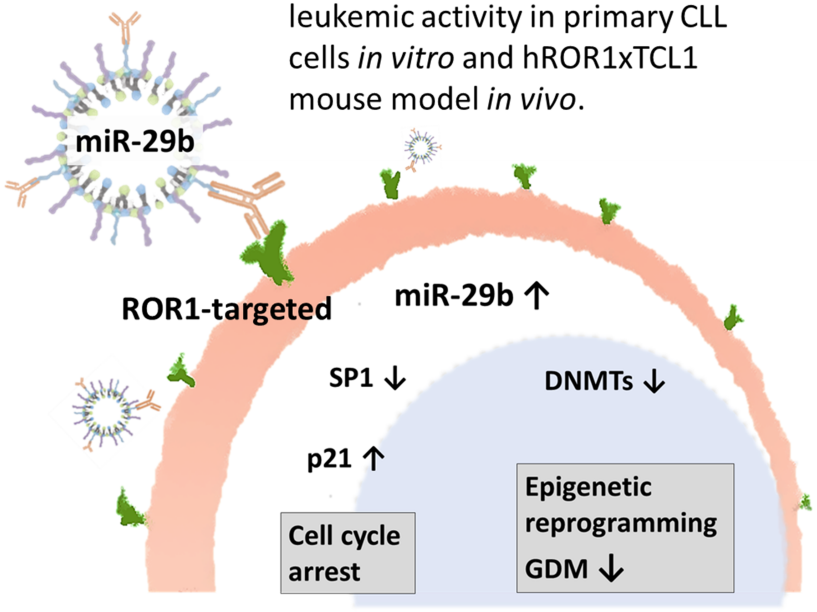


Conclusions

- Aggressive CLL expresses low miR-29b.
- ROR1 is expressed in over 95% of CLL but not normal B cells.



- Leukemia-targeted delivery of miR-29b via ROR1 exerts potent anti-leukemic activity in primary CLL cells *in vitro* and hROR1xTCL1 mouse model *in vivo*.



These studies form the basis for targeted delivery of miR therapeutics selectively to ROR1+ hematological Malignancies and solid tumors.

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Please see poster #2188 for further information