

## Epigenetic mechanisms and treatment approaches for Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is an aggressive B-cell malignancy with a poor prognosis. Over 90% of MCL cases are associated with a t(11;14) recurrent chromosomal translocation which drives the overexpression of cyclin D1 (CCND1), a critical regulator of the cell cycle. However, animal models show that CCND1 overexpression alone is insufficient to induce malignancy, suggesting that additional factors contribute to MCL development, which could inform the creation of targeted therapies. Chromosomal translocations are known to induce large-scale alterations in 3D genome organization, as well as transcriptional and epigenetic modifications at the affected loci. In this study, we reveal that in MCL cells, the translocated CCND1 locus on derivative chromosome 14 relocates to the nuclear center, coinciding with the emergence of a novel super-enhancer (SE) within the translocation breakpoint and the overall activation of the enhancer landscape. Surprisingly, we also observed that most genes upregulated in MCL were located on chr19, and not the der14. Using Hi-C and 3D-FISH, we identified an interchromosomal interaction between chr11 and chr19, primarily involving the derivative CCND1 locus. We propose that deregulated genes on chr19 contribute to MCL pathogenesis, driven in part by the MCL-specific SE within the CCND1 locus. To explore therapeutic avenues, we tested an SE-inhibitor Minnelide, in MCL models. Minnelide effectively suppressed the chromatin landscape, including the novel SE, and demonstrated strong anti-MCL activity in vitro and in vivo. These findings offer preclinical evidence and new insights into MCL pathogenesis, highlighting SE inhibition as a promising therapeutic strategy.

**Auteurs principaux:** Mlle SCHWAGER (KARPUKHINA), Anna (CNRS, UMR 9018, Université Paris-Saclay, Institut Gustave Roussy, 94800 Villejuif, France); VASSETZKY, Yegor (CNRS, UMR 9018, Université Paris-Saclay, Institut Gustave Roussy, 94800 Villejuif, France); GRISHINA, Yelena (CNRS, UMR 9018, Université Paris-Saclay, Institut Gustave Roussy, 94800 Villejuif, France)

**Orateur:** GRISHINA, Yelena (CNRS, UMR 9018, Université Paris-Saclay, Institut Gustave Roussy, 94800 Villejuif, France)