## Histone modification enzymes are critical for N-Myc-driven gene transcription and tumourigenesis

**Tao Liu**
The University of New South Wales, Australia

Myc oncoproteins exert tumorigenic effects by regulating the expression of target oncogenes. We previously show that the histone H3 lysine four presenters WDR5 promotes N-Myc-mediated gene transcription and tumour cell proliferation. Histone H3 lysine79 (H3K79) methylation at Myc-responsive elements of target gene promoters is a strict prerequisite for Myc-induced transcriptional activation. *DOT1L* is the only known histone methyltransferase that catalyses H3K79 methylation. Here, we showed that N-Myc up-regulated *DOT1L* mRNA and protein expression by binding to the *DOT1L* gene promoter. Knocking down *DOT1L* reduced mRNA and protein expression of the N-Myc target genes *ODC1* and *E2F2*. *DOT1L* bound to the Myc Box II domain of N-Myc protein, and knocking down *DOT1L* reduced histone H3K79 methylation and N-Myc protein binding at the *ODC1* and *E2F2* gene promoters and reduced neuroblastoma cell proliferation. Treatment with the small molecule *DOT1L* inhibitor SGC0946 reduced H3K79 methylation and proliferation of *MYCN* gene-amplified neuroblastoma cells. In mice xenografted with neuroblastoma cells stably expressing doxycycline-inducible *DOT1L* small hair-pin RNA, ablating *DOT1L* expression with doxycycline significantly reduced *ODC1* and *E2F2* expression, reduced tumor progression and improved overall survival. In addition, high levels of *DOT1L* gene expression in human neuroblastoma tissues correlated with high levels of *MYCN*, *ODC1* and *E2F2* gene expression, and independently correlated with poor patient survival. Taken together, our data identify *DOT1L* as a novel co-factor in N-Myc-mediated transcriptional activation of target genes and neuroblastoma oncogenesis, and *DOT1L* inhibitors as novel anticancer agents against *MYCN*-amplified neuroblastoma.

### Speaker Biography

Tao Liu is originally trained as a Medical Practitioner specializing in Neurology and an Associate Professor. He studied for a PhD degree at The University of New South Wales, Sydney, Australia on the role of inflammatory mediators in chronic pain due to nerve injury. He then worked on the role of MIC-1, a new member of the transforming growth factor beta superfamily, in cancer cell proliferation, survival/apoptosis and metastasis at St. Vincent's Centre for Applied Medical Research, Sydney, Australia. He is an Associate Professor and joined Children's Cancer Institute Australia for Medical Research ten years ago. He has been focusing his research on the roles of histone deacetylases, histone demethylases, and histone methyltransferases, BET bromodomains proteins and long noncoding RNAs in modulating gene transcription and tumourigenesis, and the roles of histone deacetylase inhibitors, histone methyltransferase inhibitors and BET bromodomain inhibitors as anticancer agents *in vitro* and in mouse models of cancer.

**e:** tliu@unsw.edu.au

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