



International Workshop on CLL  
20-23 SEPTEMBER 2019 EDINBURGH

# Cooperation between *SF3B1* mutation and *ATM* deletion in the development of CLL

A faded, light blue map of Edinburgh and its surrounding areas, including Dalmeath, Currie, Swanston, Pentlands, Lasswade, and Newbattle. The map shows various landmarks, houses, and the Caledonian Railway.

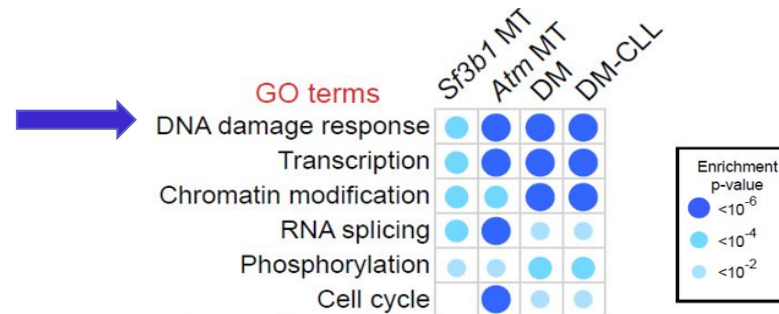
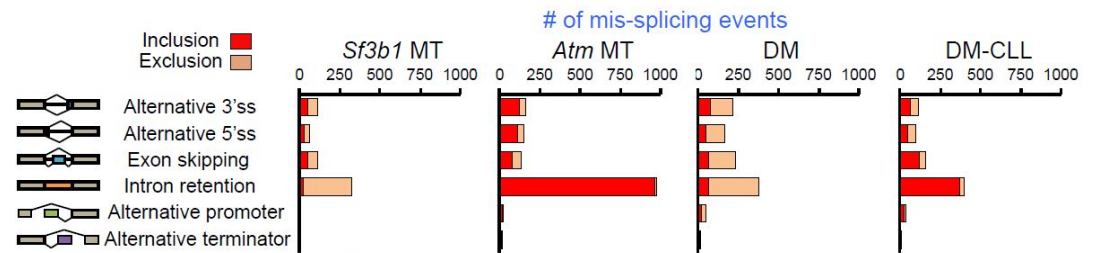
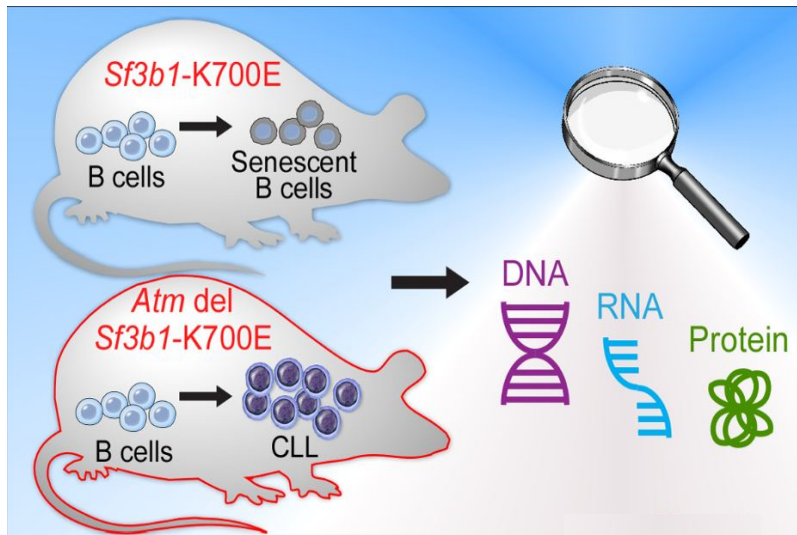
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# Disclosure

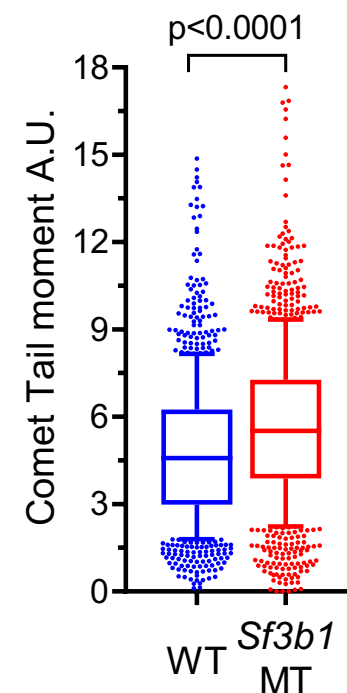
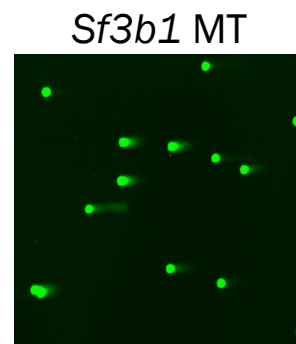
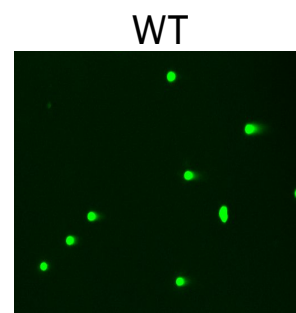
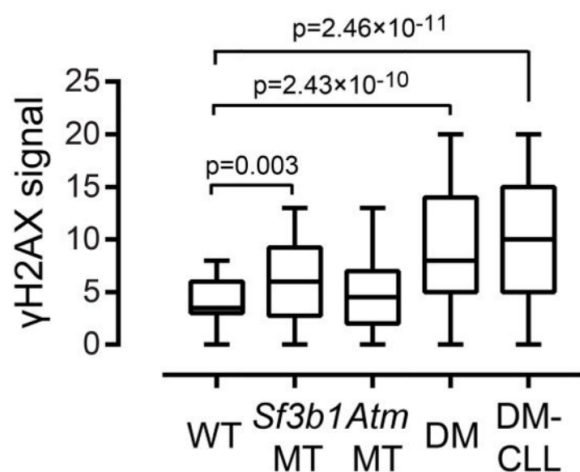
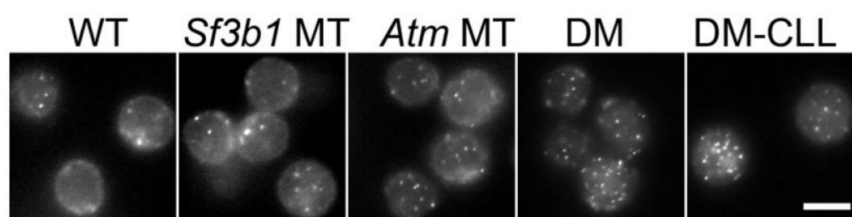
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I have no financial disclosure or conflicts of interest related to the content of this presentation

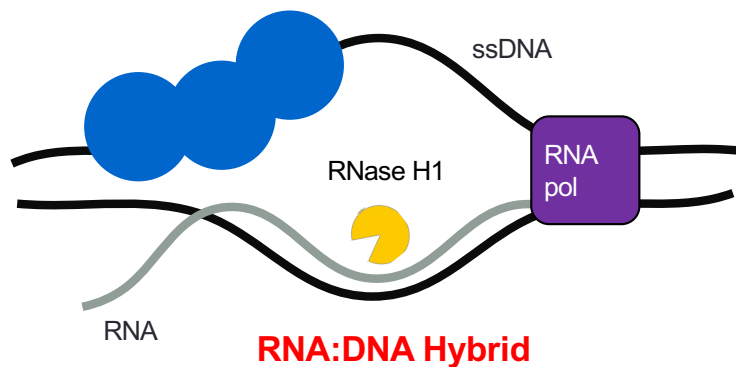
# Co-expression of *Sf3b1*-K700E and *Atm* deletion leads to CLL-like disease



# *Sf3b1* mutation and *Atm* deletion cause increased genomic instability

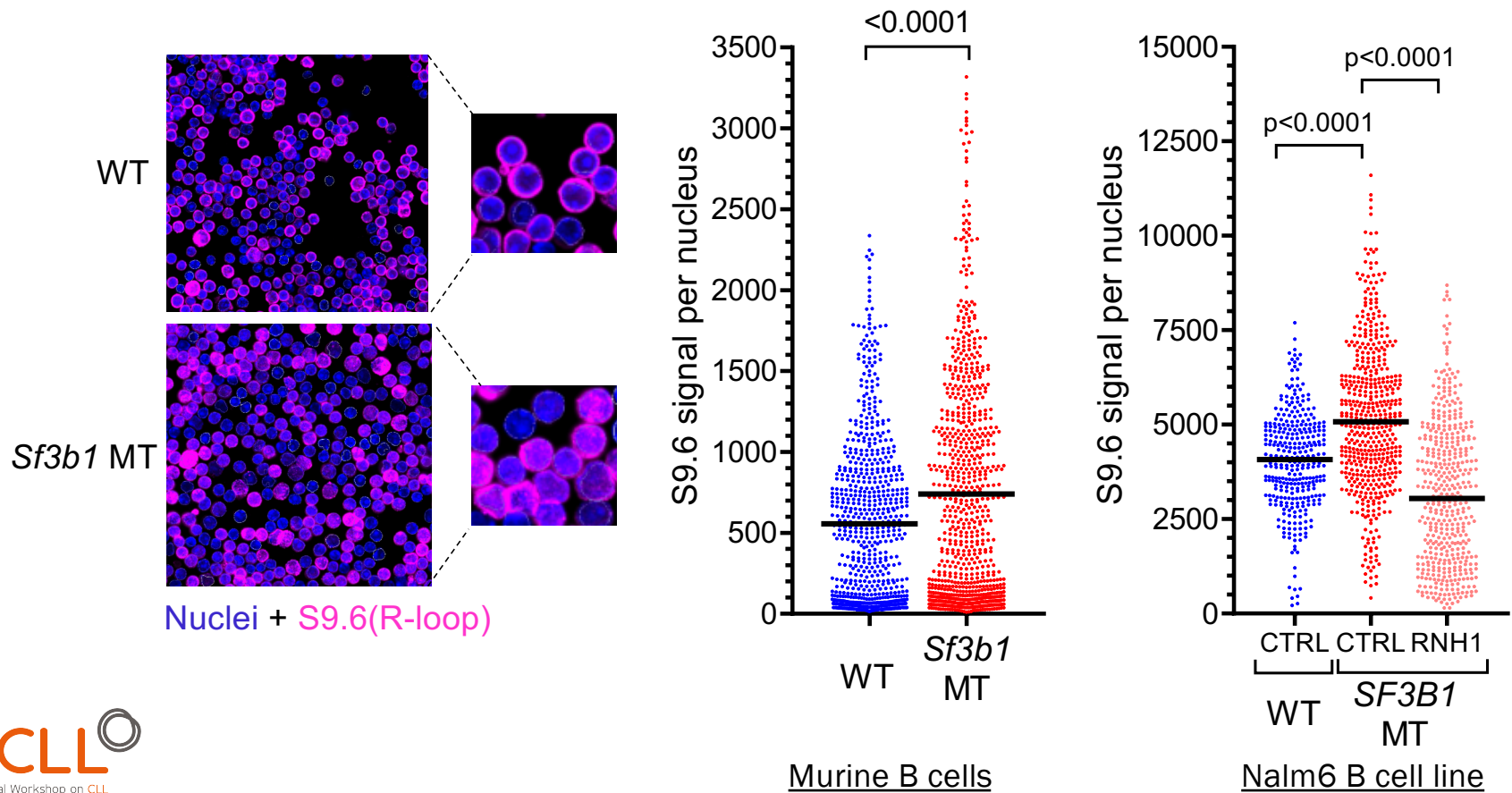


# R-loops: a link between transcription and DNA damage response

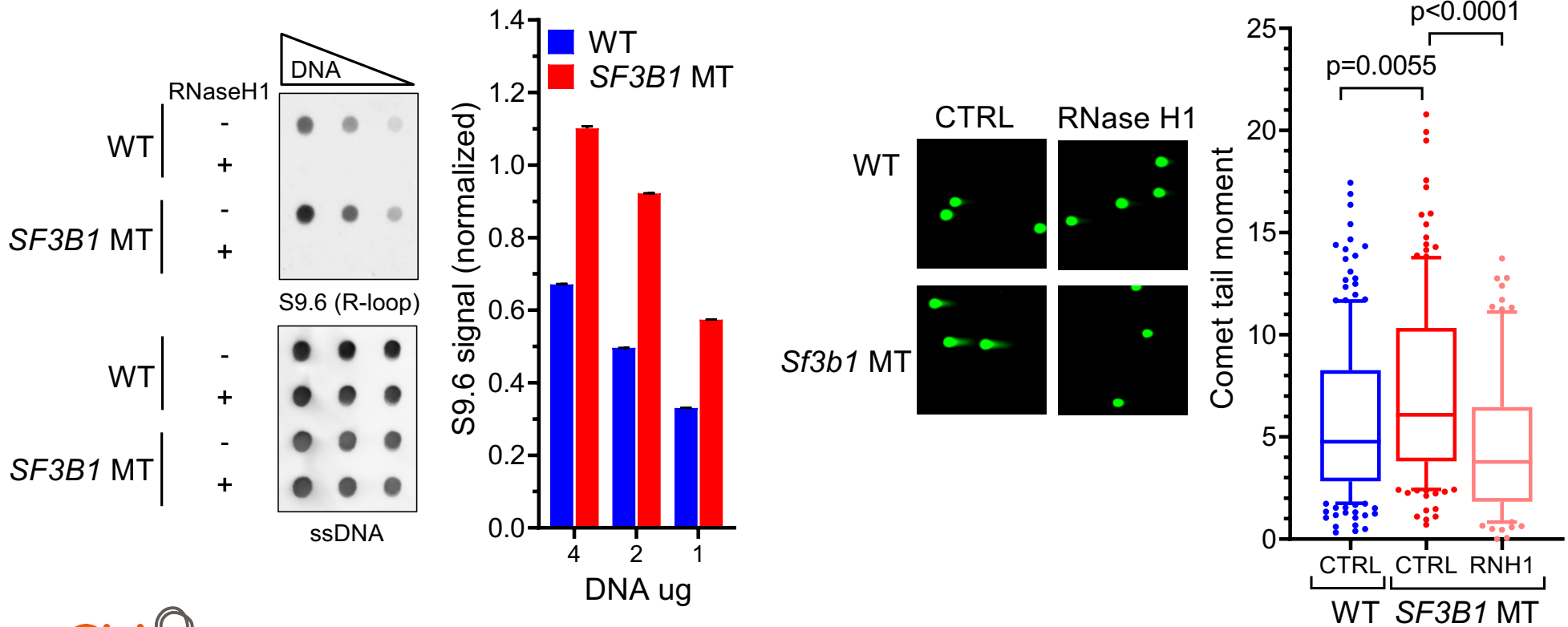


- Three stranded structure: DNA:RNA hybrid plus ssDNA displaced
- Source of replication stress and genomic instability when accumulated
- Splicing factor mutations and deletion are associated with increased R-loop formation
- Can be detected with immunoblot or immunofluorescence using S9.6 antibody
- Can be removed by RNase H1 that specifically degrades RNA in an RNA/DNA substrate

# *SF3B1* mutation induces R-loop accumulation



# *SF3B1* mutation associated DNA damage is reduced with the removal of R-loop



Nalm6 B cell line

Nalm6 B cell line

# Summary

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- *SF3B1* mutation induces R-loop accumulation and double strand breaks
- Removal of R-loop reduces the level of *SF3B1* mutation associated double strand breaks



# Acknowledgements



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