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**INVITED SPEAKER PRESENTATION** 



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# Follicular lymphomagenesis: early steps and associated risk factors

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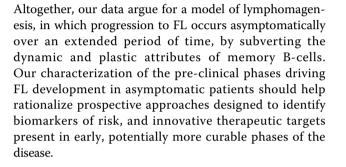
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Follicular lymphoma (FL) is a mature B-cell neoplasm resulting from the transformation of germinal center (GC) B-cells in secondary lymphoid organs. The acquisition of the t(14;18) chromosomal translocation (giving rise to a BCL2/IGH fusion and ectopic expression of the BCL2 proto-oncogene) constitute both a genetic hallmark and the critical early event in the natural history of FL [1]. However, as t(14;18) is detectable at low frequency (<1 per million B-cells) in up to 70% of healthy people, the relationship between t(14;18) and progression to disease remains unclear [2]. To date, the available data supports a multi-hit model of oncogenesis, where the stepwise acquisition of synergistic oncogenic events is required for full malignant transformation. The recent demonstration that memory B-cells can re-enter GCs and participate to new rounds of GC reactions has opened the possibility that multi-hit B-cell lymphomagenesis gradually occurs throughout life during successive immunological challenges[3-5]. Here we provide evidence for this scenario in FL using a sporadic BCL2<sup>tracer</sup> mouse model mimicking FL's hallmark t(14;18) translocation, combined with molecular/immunofluorescent tracking of  $t(14;18)^+$  clones and normal memory B-cells in paired lymphoid tissue samples from healthy individuals.

We show that BCL2-expressing memory B-cells require multiple GC transits to acquire the distinctive FL-like maturation arrest as GC B-cells with constitutive activation-induced cytidine deaminase activity, and to progress to advanced precursor stages.

This protracted process of GC co-opting, accumulating with age, would drive the major and early dissemination/ progression of  $t(14;18)^+$  precursors observed in remote lymphoid tissues, including bone marrow, shaping the systemic disease presentation observed in most patients.

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