XIX CONGRESSO NAZIONALE SIES2026
Firenze | 4-6 marzo 2026
Palazzo degli Affari

XIX Congress of the Italian Society of Experimental Hematology ABSTRACT N. CO11

Chronic lymphocytic leukemia and Chronic Lymphoproliferative Disorders

BCOR INACTIVATION IN B CELLS INITIATES CLL-LIKE DISEASE AND ENABLES STUDY OF DISEASE EVOLUTION IN A NOVEL MOUSE MODEL

D. Sorcini[1], A. Stella[1], F.M. Adamo[1], F. De Falco[1], R. Arcaleni[1], F. Gurrieri[1], E. Dorillo[1], A. Esposito[1], L. Valmarini[1], A. Atzeni[1], B. Bigerna[2], M.P. Martelli[1|2], P. Sportoletti[1|2]

[1]Department of Medicine and Surgery, Institute of Hematology and Center for Hemato- Oncology Research CREO, University of Perugia and Santa Maria della Misericordia Hospital; [2]Santa Maria della Misericordia Hospital.

Introduction: CLL is a mature B cell CD19+CD5+ malignancy driven by genetic and microenvironmental factors promoting survival and therapy resistance. Despite advances, it remains incurable, stressing the need for preclinical models mimicking disease biology. BCL6 co-repressor (BCOR) loss-of-function mutations occur in ~2% of CLL, often with unmutated IGHV, trisomy 12, and NOTCH1 mutations (Sportoletti et al., Blood 2021). We previously showed that BCOR loss contributes to Richter Transformation in TCL1 mice (Rompietti et al., Leukemia 2025). In young mice, BCOR deletion disrupts B cell homeostasis without causing disease. To determine if BCOR loss alone initiates CLL, we performed a longitudinal analysis of a B cell–specific BCOR knockout model.

Methods: We generated BCOR null mice by crossing Bcorflox with CD19-Cre transgenic mice. Homozygous (Bcorflox/flox;Cre$^+$) and hemizygous (Bcorflox/Y;Cre$^+$) mice were referred as CD19Bcor−/−. Peripheral blood (PB), bone marrow (BM) and spleen were analyzed by flow cytometry (FC), blood counts and histopathology. Clonality was assessed via IGH rearrangement in sorted CD19+CD5+ splenic B cells. Disease transplantability was tested by injecting splenic cells into NSG recipients.

Results: In long-term follow-up, CD19Bcor−/− mice showed reduced overall survival compared to wild-type (WT) controls (Bcorflox/flox;Cre− and Bcorflox/Y;Cre−), with a median survival of 762.5 days (range 510–821). Full blood counts at 22–28 months showed elevated white blood cell levels in CD19Bcor−/− mice (12.91±0.99×10^3/μL;N=17) vs WT (9.16±1.20×10^3/μL;N=14). FC of PB, spleen, and BM revealed marked expansion of CD19+CD5+ B cells in mutants compared to WT: PB (538.1±351.3 vs 63.41±16.76 cells/μL), spleen (16.35×10^6±4.72 vs 3.23×10^6±0.99 cells), and BM (1.91×10^6±0.74 vs 0.37×10^6±0.08 cells). Histology of moribund mice revealed diffuse infiltration of liver, spleen, lung, and kidney by small, monomorphic lymphoid cells, identified as CD19+CD5+ by FC. IGH gene rearrangement analysis of sorted CD19+CD5+ splenic cells showed a monoclonal population. All data supported diagnosis of a lymphoproliferative disorder resembling low-grade CLL. To assess disease propagation, splenic cells from CD19Bcor−/− mice were transplanted into NSG mice, which developed CLL-like disease with CD19+CD5+ expansion. 60 days after primary transplant, (38.6 ± 12.3 cells/μL;N=4) were detected in PB; secondary transplant yielded higher burden (532.3 ± 192.8 cells/μL at 50 days;N=4), indicating accelerated disease. Histology confirmed spleen and liver infiltration, more aggressive in secondary recipients, suggesting clonal evolution. This model mirrors indolent and aggressive CLL phases and enables study of progression. Ongoing RNA-seq analyses aim to define BCOR-driven programs and identify signatures shared with BCOR-mutated CLL patients.

Conclusions: CD19Bcor−/− mice represent a novel preclinical model of CLL, enabling studies on disease evolution and therapeutic targeting.