Targeting the tumor microenvironment in chronic lymphocytic leukemia

Rebecka Svanberg,1* Sine Janum,2* Piers E.M. Patten,3 Alan G. Ramsay3 and Carsten U. Niemann1

1Department of Hematology, Rigshospitalet, Copenhagen, Denmark; 2Department of Clinical Haemato-oncology, Bartholomew’s Hospital, Barts Health Trust, London, UK; 3School of Cancer and Pharmaceutical Sciences, Faculty of Life Sciences & Medicine, King’s College London, London, UK

*RS and SJ contributed equally as co-first authors.

©2021 Ferrata Storti Foundation. This is an open-access paper. doi:10.3324/haematol.2020.268037

Received: August 6, 2020.
Accepted: March 31, 2021.
Pre-published: April 22, 2021.
Correspondence: CARSTEN UTOFT NIEMANN - carsten.utoft.niemann@regionh.dk
Supplementary figures.

Supplementary figure 1.
Supplementary figure legend.

**Supplementary figure 1. Selection of key CLL-TME constituents and interactions.**
CD4+ T-cells mediate tumor support, for example through cytokine signaling and CD40/CD40L co-stimulation. Chronic activated/exhausted T-cells have increased expression of PD-1. Increased number of T<sub>Reg</sub>s contribute to suppressing T-cell function. CLL cells promote MDSCs, which, in turn, suppress T-cell effector function and promote T<sub>Reg</sub> differentiation. Bidirectional chemokine signaling between macrophages or stromal cells and CLL cells promote migration of CLL cells into protective niches. Adhesion molecules on CLL cells (LFA-1) bind to stromal cell receptors (ICAM-1). BAFF provided by for example NLCs stimulate BAFF-R on CLL cells, promoting survival and growth. CLL cells recruit and modulate their microenvironment by secretion of for example cytokines, chemokines, and EVs. CLL, chronic lymphocytic leukemia; TME, tumor microenvironment; BCR, B-cell receptor; CD, cluster of differentiation; CD40L, CD40 ligand; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein-1 ligand; CCL2, chemokine ligand 2; EVs, extracellular vesicles; LFA-1, lymphocyte function-associated antigen 1; ICAM-1, intercellular adhesion molecule 1; CXCL12, CXC motif chemokine 12; CXCR4, CXC chemokine receptor 4; BAFF, B-cell activating factor; BAFF-R, B-cell activating factor receptor; IL, interleukin; NLCs, nurse like cells; TAMs, tumor associated macrophages; MDSCs, myeloid derived suppressor cells; T<sub>Reg</sub>, regulatory T-cell.