Project Title: Modeling childhood leukemia target treatment.

Background: Acute lymphoblastic leukemia (ALL) is the most frequent cancer in children. It is a heterogeneous disease driven by distinct genetic alterations. At present, the cure rates for children with ALL is >80%, while 20% of patients still experience relapse, with a favorable outcome of only 30%. In particular, three genetic subgroups are associated with a high-risk of disease relapse, namely ALL patients with Down Syndrome and patients with alterations of the PAX5 gene. Despite the development of intensive multidrug therapeutic protocols, those patients still suffer from a low cure rate. Therefore, the development of tailored therapeutic strategies is a formidable challenge for these genetic subgroups of patients.

Preliminary data: i) We identified specific genomic lesions in DS-ALL cases, and contributed to elucidate the prognostic role of CRLF2 rearrangements, a frequent alteration in DS-ALL. Our in vitro preliminary data suggest that Givinostat is able to kill ALL cell lines with CRLF2 alteration (MUTZ5 and MHH-CALL4) at low concentrations and to block the JAK/STAT signaling pathway. Moreover, Givinostat resulted to be more effective compared with more specific JAK2 inhibitors (i.e. Ruxolitinib). ii) We recently identified novel PAX5 fusion genes and expanded primary cells in mice xenotransplants. We demonstrated that PAX5 fusions lead to overexpression of lymphocyte-specific protein tyrosine kinase (LCK), which in turn results in STAT5 hyper-activation and we setup LCK targeting experiments ex-vivo, using LCK specific inhibitor BIBF1120.

Objectives and scientific expected results: Frontline identification of targetable lesions in ALL patients and testing in vitro and in vivo the efficacy of new drugs in high-risk cases.
i) In DS-ALL cases bearing alterations of the CRLF2 pathway, we will evaluate the possibility to decrease the doses of the current multichemotherapy approach with the introduction of a more specific, effective and less toxic drug (Givinostat). A new promising JAK2 inhibitor in also available for testing.
ii) In cases with PAX5 rearrangements we aim at targeting the aberrant signaling pathways using the LCK inhibitor BIBF1120 in xenotransplantion mice models.

Expected project outcome: This study will allow to better dissect the functional pathogenesis of genetic lesions in DS-ALL and ALL cases with PAX5 lesions. Importantly, we expect to identify specific compounds functionally efficient for these genetic subgroups of patients under investigation, including already FDA-approved drugs in Clinical Trials for other diseases (as Givinostat in myeloproliferative disorders and juvenile idiopathic arthritis; BIBF1120 in several solid tumors). In all settings, we expect to validate the efficacy of the compounds in a preclinical model using immune-deficient mice transplanted with patients-derived primary samples.

Expected Results in terms of training: The ESR will be working in a team working in these projects and she/he will gain expertise in molecular and cellular biology approaches: retrovirus-mediated expression, NGS sequencing, advanced flow cytometry techniques xenotranplantation, drug testing. The ESR will be enrolled in the PhD Program in Translational and Molecular Medicine - DIMET at the University of Milano-Bicocca http://www.dimet.org/