

 <p><b>UniSR</b> Università Vita-Salute San Raffaele</p>	<p><b>APPLICATION TO ACT AS SUPERVISOR AND RESEARCH PROJECT PROPOSAL</b></p>	<p><b>MO 20-5</b> ed. 01 del 21/02/2025 PO 20 Page 4 of 11</p>
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**PROJECT**

**Supervisor:** GHIA PAOLO PROSPERO

Title: Exploring TPL2 involvement in CLL pathogenesis

Curriculum: BAIO

Link to the personal page of the University or relevant hospital site website: <https://research.hsr.it/en/divisions/experimental-oncology/b-cell-neoplasia.html>

<https://www.unisr.it/docenti/g/ghia-paoloprospero>

**Description of the Project (max 3,000 characters including spaces)**

**Background/gap of knowledge**

Tumor Progression Locus 2 (TPL2) is a protein that has been recently implicated in inflammation and cancer [1,2] as well as in the regulation of immune functions[2]. It plays a role in the regulation of the mitogen-activated protein kinase (MAPK) signaling pathway by directly phosphorylating MEK, which in turn activates ERK. Interestingly, dysregulation of the MAPK signaling pathway has been reported in Chronic Lymphocytic Leukemia (CLL) [3,4] potentially being implicated in the development and progression of the disease. This dysregulation can occur through various mechanisms, including genetic mutations, alterations in upstream regulators, or interactions with the CLL microenvironment. TPL2 shows a dual role in cancer: on the one hand, some studies have demonstrated that elevated TPL2 kinase activity is connected to inflammatory diseases and acts as a strong promoter of tumor growth in various human cancers [2,5]; on the other hand, suppressed TPL2 expression has also been reported in different tumor types and its ablation is associated with increased tumorigenesis in several experimental cancer models, being required for optimal p53 response to genotoxic stress [5,6].

**Rationale and hypothesis**

TPL2 has been found downregulated in patients with CLL and in particular in patients belonging to subgroups associated with shorter overall survival (OS) and time to first treatment. Initial analysis of public datasets reveals that *TPL2* expression levels directly correlates with OS and Failure-free survival (FFS), strengthening the hypothesis that the reduction of TPL2 might play a role in the natural history of CLL. The functional relevance of TPL2 reduction in CLL is, to date, unexplored, but it is of utmost interest to understand at the molecular level the mechanisms



through which reduced TPL2 is involved in more aggressive clinical behavior and validate it as a potential new target for a personalized medicine approach.

### **Objectives and specific aims**

The aim of the project is to investigate the functional consequences of *TPL2* ablation in CLL and how it may impact disease evolution and aggressiveness. In particular, we are planning to investigate:

- the effect of *TPL2* ablation on cell proliferation, BcR signaling, resistance to apoptosis in human CLL cell lines and in murine models of CLL
- the functional impact at the transcriptional level associated with *TPL2* downregulation in CLL cells (human cell lines, primary samples, and murine leukemic cells)
- the potential contribution, of *TPL2* downregulation in leukemic cells, in shaping the supportive tumor microenvironment

### **Expected outcomes**

The results of this study have the potential to identify new ways to risk-stratify patients and test new tailored treatment modalities. In particular, we aim to discover new biomarkers that can enhance our current prognostic capacity and identify molecules that may be used as new therapeutic targets.

### **Skills that the student should acquire** (max. 600 characters including spaces):

The student will acquire deep knowledge of the molecular mechanisms responsible for the development of B cell lymphoproliferative disorders, practical expertise in cellular biology including handling, purification and sorting of primary human and murine cells, in molecular biology, including CRISP/CAS technology, as well as in mouse handling. The student will also become proficient in design and management of scientific projects and in data presentation and discussion.

### **References** (max. 15)

1. Xu D, Matsumoto ML, McKenzie BS, Zarrin AA. TPL2 kinase action and control of inflammation. Vol. 129, Pharmacological Research. Academic Press; 2018. p. 188–93.



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2. Njunge LW, Estania AP, Guo Y, Liu W, Yang L. Tumor progression locus 2 (TPL2) in tumor-promoting inflammation, tumorigenesis and tumor immunity. Vol. 10, Theranostics. Ivyspring International Publisher; 2020. p. 8343–64.
3. Landau DA, Tausch E, Taylor-Weiner AN, Stewart C, Reiter JG, Bahlo J, et al. Mutations driving CLL and their evolution in progression and relapse. Nature. 2015 Oct 22;526(7574):525–30.
4. Ecker V, Brandmeier L, Stumpf M, Giansanti P, Moreira AV, Pfeuffer L, et al. Negative feedback regulation of MAPK signaling is an important driver of chronic lymphocytic leukemia progression. Cell Rep. 2023 Oct 31;42(10).
5. Decicco-Skinner KL, Trovato EL, Simmons JK, Lepage PK, Wiest JS. Loss of tumor progression locus 2 (tpl2) enhances tumorigenesis and inflammation in two-stage skin carcinogenesis. Oncogene. 2011 Jan 27;30(4):389–97.
6. Gkirtzimanaki K, Gkouskou KK, Oleksiewicz U, Nikolaidis G, Vyrla D, Liontos M, et al. TPL2 kinase is a suppressor of lung carcinogenesis. Proc Natl Acad Sci U S A. 2013 Apr 16;110(16).