Pablo Oppezzo, PhD
Head of Research Laboratory
on Chronic Lymphocytic Leukemia
Institut Pasteur de Montevideo, Uruguay
e-mail: poppezzo@pasteur.edu.uy

Personal Statement

PhD in Immunology at University Paris VI, and post-doctorate at the Institut Pasteur in Paris, France. He is the Principal Investigator of the Research Laboratory on Chronic Lymphocytic Leukemia at Institut Pasteur de Montevideo, Uruguay. Dr. Oppezzo has published more than 50 scientific papers in high impact factor journals such as Blood, Leukemia and Cancer Research. Dr. Oppezzo's research focuses on the mechanisms involved in progression of B-cell malignancies, specifically in Chronic Lymphocytic Leukemia (CLL). He created the first CLL research group in Uruguay coordinating a CLL network through the CYTED international project (Programa Ibero Americano de Ciencia y Tecnología para el Desarrollo) between 2011 and 2014. Dr. Oppezzo has been member of the international scientific committee for the Young Investigators Meeting during the International CLL workshop and a member of the scientific and organizing committees of the IberoAmerican CLL meetings. He is co-founder of the Latin American Group on CLL (LAG-CLL) which aims to build a network supporting new collaborations between clinical, biological and pharmaceutical groups working in South America.

Contribution to Science

The major focus of his research has been the study of the mechanisms involved in the progression of CLL disease. The B cell is one of the most specialized cells and it has the ability to re-edit its DNA in order to diversify the repertoire of immunoglobulins. This action is totally dependent on the enzyme activation-induced cytidine deaminase (AID). Since these events are essential for a successful immune response, the B lymphocyte is continuously exposed to a dangerous mutagenic mechanism that should be tightly regulated. Our advances in this area are related to the characterization of AID expression in progressive patients with CLL. This molecule is involved not only in the immunoglobulin diversification process, but is also related to oncogenic events. We were one of the first to report the anomalous expression of AID in the peripheral blood of progressive CLL patients (**Oppezzo et al., Blood, 2003)** and we described that its expression is tightly regulated by a spliced form of the transcription factor Pax-5a **(Oppezzo et al., Blood, 2005).** Next, we reported that AID expression in CLL B cells is mainly confined to a small and proliferative subset of tumor cells ongoing class switch recombination (IgM/IgG positive cells, *i.e.* proliferative fraction – PF-) **(Palacios et al., Blood, 2010),** and finally characterized the molecular mechanism underlying the proliferative behavior of this subset, **(Palacios et al, Leukemia 2015 and Palacios et al. Leukemia & Lymphoma, 2015)**.

Subsequently, we developed a double transgenic mouse model (TCL1/AID) emulating unmutated progressive CLL patients that over-express AID, **(Morande P., Leukemia & Lymphoma, iwCLL-2015, Sydney, Australia and iwCLL-2017, New York, USA)** and demonstrated that AID overexpression in this model leads to aggressive murine CLL and non-Ig mutations that mirror human neoplasms. We also studied plasma-derived exosomes of progressive CLLs with PFs at the proteomic level and found that in an inflammatory context the leukemic clone is able to express high amounts of S100A9 protein which in turn is able to activate NF-κB signaling, one of the main pathways responsible for AID expression **(Prieto, et al. Blood, 2017).** In our more recent work we focused on the effects of new drugs such as Ibrutinib targeting PF. Our results show that AID expression and PFs are decreased during ibrutinib therapy, and that downregulation of AID is associated with a decrease in JAK1/STAT6 signaling, **(Morande et al, et al. Blood, 2019).**

Altogether, these results led us to propose a working hypothesis in which AID overexpression in proliferating CLL fractions is a consequence of a continuous stimulation of the tumor clone in an inflammatory microenvironment and that, targeting of these proliferative subsets appears to have therapeutic value.