



CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150277

Project Title:
Vertical targeting of the B cell receptor in leukemia and lymphoma

Award Mechanism:
Individual Investigator

Principal Investigator:
Aguiar, Ricardo

Entity:
The University of Texas Health Science Center at San Antonio

Lay Summary:

Mature B cell tumors (non-Hodgkin's lymphoma, chronic lymphocytic leukemia, multiple myeloma) are associated with a poor outcome highlighting an unmet medical need for new therapies. These cancers are driven, in part, by the B cell receptor (BCR). We previously showed that downmodulation of the phosphodiesterase 4 (PDE4) can inhibit the BCR signals and reduce the growth of B cell cancers. These observations led us to open a clinical trial of Roflumilast (a FDA-approved PDE4 inhibitor) in patients with B cell lymphomas and leukemia. To date, five patients have been enrolled in the study and early signs of clinical benefit have already been observed. We now plan to build upon these early successes by testing the hypothesis that the anti-tumor activity associated with PDE4 inhibition derives from the suppression of the BCR-related protein kinases, BTK and PI3KDelta. By extension, we propose that combining PDE4 inhibitors with agents that target these kinases will impart clinical benefit. To achieve these goals, we developed a specific mouse model with genetic loss of PDE4 in a lymphoma-prone background. Here, we will first assess the impact of PDE4 deletion on cancer growth and on the activity of the downstream pathways controlled by the BCR. Next, we will use this mouse model to pre-clinically test the benefits of combining Roflumilast with BTK or PI3KDelta inhibitors; this strategy should result in improved anticancer activity and limit the acquisition of therapeutic resistance. Lastly, we will expand our ongoing clinical trial of Roflumilast in patients with B cell tumors by analyzing the effects of this agent on the activity of BCR pathway in the cancer cells – we propose that suppression of this pathway will function as a biomarker for clinical response. When these studies are completed, we plan to test in the clinic a novel approach for the treatment of patients with B cell cancers – namely the combination of PDE4 and BCR-related kinase inhibitors.