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Emrah Ilker Ozay
University of Massachusetts Amherst

Gabriela Gonzalez-Perez
University of Massachusetts Amherst

Joe Torres
University of Massachusetts Amherst

See next page for additional authors

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Anti-pPKCθ (T538) Delivery via Cell Penetrating Peptide Mimics as a Novel Treatment of Aplastic Anemia

Emrah Ilker Ozay¹,²,³, Gabriela Gonzalez-Perez², Joe Torres¹,² Gregory N. Tew¹,²,³, and Lisa M. Minter¹,²

¹Program in Molecular and Cellular Biology, ²Department of Veterinary and Animal Sciences, ³Department of Polymer Science and Engineering, University of Massachusetts, Amherst, MA, 01003

Contact information: eozay@mcb.umass.edu

The objective of this study is to deliver anti-pPKCθ (T538) into T cells (hPBMCs) by using cell penetrating peptide mimics (CPPMs) to neutralize PKCθ activity both in vitro and in vivo, with the eventual goal of treating aplastic anemia (AA). AA is an immune-mediated bone marrow failure disease caused by T helper type 1 (Th1) autoimmune responses, which destroy blood cell progenitors. It was previously reported that protein kinase C theta (PKCθ), expressed specifically in T cells, plays an important role in T cell signaling by mediating Th1 differentiation. Mice treated with Rottlerin, a pharmacological inhibitor of PKCθ, are rescued from the disease when PKCθ phosphorylation was inhibited. Furthermore, humanized antibodies are increasingly gaining attention as therapies. The delivery of antibodies could be achieved via cell penetrating peptides (CPPs), which are able to internalize cargo into cells. Here, we designed, synthesized and characterized CPPMs to increase delivery efficiency of an antibody against phosphorylated PKCθ (T538), which subsequently interfered with the function of the kinase. We designed an in vitro delivery method for the CPPM/Anti-pPKCθ complex then assessed T cell activation and AA disease marker expression. Also, we generated an in vivo humanized mouse model of AA and tested the complex for delivery and effect on survival of these mice. Altogether the results reveal that PKCθ may be an optimal target for bone marrow failure treatment and intracellular antibody delivery may represent a novel approach for AA treatment.