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Et al.

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

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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.