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## Anti-pPKC $\theta$ (T538) Delivery via Cell Penetrating Peptide Mimics as a Novel Treatment of Aplastic Anemia


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## **Anti-pPKC $\theta$ (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-pPKC $\theta$  (T538) into T cells (hPBMCs) by using cell penetrating peptide mimics (CPPMs) to neutralize PKC $\theta$  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 (PKC $\theta$ ), 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 PKC $\theta$ , are rescued from the disease when PKC $\theta$  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 PKC $\theta$  (T538), which subsequently interfered with the function of the kinase. We designed an *in vitro* delivery method for the CPPM/Anti-pPKC $\theta$  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 PKC $\theta$  may be an optimal target for bone marrow failure treatment and intracellular antibody delivery may represent a novel approach for AA treatment.