

**A-Kinase Anchoring Proteins associate with Phosphodiesterases in T lymphocytes**Asirvatham AL<sup>1</sup>, Galligan S<sup>1</sup>, Schillace RV<sup>1</sup>, Vasta V<sup>2</sup>, Beavo JA<sup>2</sup> and Carr DW<sup>1</sup>.<sup>1</sup>Department of Veterans Affairs Medical Center, Department of Endocrinology, Oregon Health and Sciences University, Portland, OR 97239<sup>2</sup>Department of Pharmacology, University of Washington, Seattle, WA 98195

The cAMP-Protein Kinase A (PKA) pathway in T cells transmits an inhibitory signal to suppress T cell activation. Current investigations on cell-specific signaling have demonstrated that A-Kinase anchoring proteins (AKAPs) are involved in anchoring PKA to specific intracellular targets, thereby regulating cAMP-mediated signaling. In addition to binding PKA, AKAPs also bind other signaling molecules such as phosphodiesterases (PDE). Phosphodiesterases regulate cAMP homeostasis by hydrolyzing cAMP to AMP. Recent studies conducted by Dodge and colleagues and Tasken et al have demonstrated that PDE4D interacts with AKAPs in ventricular myocytes and Sertoli cells. Additionally, PDE7 has been documented to play an important role in T cell activation. Therefore, we hypothesize that AKAPs associate with PDEs in T lymphocytes to regulate cAMP-mediated signal transduction. To test our hypothesis, Jurkat cell lysates were immunoprecipitated with antibodies against the regulatory subunit of PKA (RII) and various AKAPs and analyzed for PDE activity. The activity of PDE associated with RII and AKAPs 95,149 and MTG16b was significantly greater compared to control (IgG). Immunoprecipitation, pull down and Western analysis illustrate an isoform specific association of PDE with AKAPs. For example, PDE4A binds to AKAP149, 95 and MTG16b but not AKAP79, and PDE7A binds to MTG16b but not AKAP149 or 79. Mapping studies have identified the PDE7A binding domain of MTG16b to be located between bases 700-1510 (amino acid 160-432). These studies confirm our hypothesis that AKAPs associate with PDEs in T cells. Further studies will determine if this association regulates cAMP-mediated inhibition of T lymphocyte activation.