Trinath J, Hegde P, Sharma M, Maddur MS, Rabin M, Vallat JM, Magy L, Balaji KN, Kaveri SV and Bayry J. 2013. Intravenous immunoglobulin expands regulatory T cells via induction of cyclooxygenase-2-dependent prostaglandin E2 in human dendritic cells. *Blood* 122:1419-1427.

CD4(+)CD25(+)FoxP3(+) regulatory T cells (Tregs) play a critical role in the maintenance of immune tolerance. Intravenous immunoglobulin (IVIg), a therapeutic preparation of normal pooled human IgG, expands Tregs in various experimental models and in patients. However, the cellular and molecular mechanisms by which IVIg expands Tregs are relatively unknown. As Treg expansion in the periphery requires signaling by antigen-presenting cells such as dendritic cells (DCs) and IVIg has been demonstrated to modulate DC functions, we hypothesized that IVIg induces distinct signaling events in DCs that subsequently mediate Treg expansion. We demonstrate that IVIg expands Tregs via induction of cyclooxygenase (COX)-2-dependent prostaglandin E2 (PGE2) in human DCs. However, costimulatory molecules of DCs such as programmed death ligands, OX40 ligand, and inducible T-cell costimulator ligands were not implicated. Inhibition of PGE2 synthesis by COX-2 inhibitors prevented IVIg-mediated Treg expansion in vitro and significantly diminished IVIg-mediated Treg expansion in vivo and protection from disease in experimental autoimmune encephalomyelitis model. IVIg-mediated COX-2 expression, PGE2 production, and Treg expansion were mediated in part via interaction of IVIg and F(ab')2 fragments of IVIg with DC-specific intercellular adhesion molecule-3-grabbing nonintegrin. Our results thus uncover novel cellular and molecular mechanism by which IVIg expands Tregs.