# An Engineered Immunomodulatory IgG1 Fc Suppresses Autoimmune Inflammation Through Pathways Shared With IVIG

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Immunoglobulin G (IgG) antibodies in the form of high-dose intravenous immunoglobulin (IVIG) exert immunomodulatory activity and are used in this capacity to treat inflammatory and autoimmune diseases. However, due to high costs and recent global shortages of IVIG, alternative therapies are desirable in the clinic. Reductionist approaches have revealed that terminal sialylation of the single asparagine (N)-linked glycan at position 297 of the IgG1 Fc bestows anti-inflammatory activity, which can be recapitulated by introducing a F241A point mutation in the IgG1 Fc ($Fc^{F241A}$). Here, we examined the anti-inflammatory activity of CHO-K1 cell-produced $Fc^{F241A}$ *in vivo* in models of autoimmune inflammation and found protection to be independent of sialylation. On the other hand, sialylation markedly improved the half-life and bioavailability of $Fc^{F241A}$ via impaired interaction with the asialoglycoprotein receptor ASGPR. Further, $Fc^{F241A}$ suppresses inflammation through the same molecular pathways as IVIG and sialylated IgG1 Fc, requiring the murine C-type lectin SIGN-R1 and its human orthologue DC-SIGN *in vitro* and SIGN-R1 *in vivo*. This contrasts with $Fc^{Abdeg}$ (Efgartigimod), an engineered IgG1 Fc with enhanced neonatal Fc receptor (FcRn) binding, which reduces total serum IgG concentrations, independent of SIGN-R1. When co-administered, $Fc^{F241A}$ and $Fc^{Abdeg}$ exhibited combinatorial anti-inflammatory activity. Together, these results demonstrate that the anti-inflammatory activity of $Fc^{F241A}$ requires SIGN-R1, similar to high-dose IVIG and sialylated IgG1, and can be used in combination with other therapeutics that rely on divergent pathways, including $Fc^{Abdeg}$, with enhanced therapeutic effects.