demonstrated the specific modulation of several genes by direct effect of aPLs. *In vivo* Qred supplementation of APS patients for one month significantly improved the monocytes' atherothrombotic gene profile, reversing the altered expression of a number of genes related to thrombosis, atherosclerosis, inflammation, oxidative stress, and intracellular signalling.

Conclusions: 1. Gene expression profile allowed the identification of relevant genes and pathways altered in monocytes of APS patients, which are associated with the pathogenesis of the disease and modulated, at least partially, by aPLs. 2. We have branded novel and specific mRNAs related to CVD in APS monocytes, further modified by effect of *in vivo* Qred supplementation.

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FRI0268 **GLUCOCORTICOID-INDUCED LEUCINE ZIPPER (GILZ) REPRESENTS A CHECKPOINT LIMITING TYPE I INTERFERON (IFN) PRODUCTION IN SLE**

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Background: Glucocorticoids (GC) remain the mainstay of treatment in Systemic Lupus Erythematosus (SLE). Type I interferons (IFN), produced by plasmacytoid dendritic cells (pDC) in response to Toll-Like receptors (TLR) ligands, are critical to SLE pathogenesis, but are not suppressed by GC. Glucocorticoid-Induced Leucine Zipper (GILZ) is an endogenous anti-inflammatory protein induced by GC. Beaulieu et al., 2010 However, whether GILZ regulates IFN production in SLE is not known.

Objectives: To test the hypothesis that GILZ inhibits the production of Type I IFN in SLE.

Methods: We performed *in vitro* analysis on pDC and bone marrow-derived DC (BMDC), and *in vivo* studies, of WT and GILZ-/- mice using stimuli of TLR7 (Imiquimod), TLR7/8 (Resiquimod) and TLR9 (CpG). IFN was measured using a IFN luciferase assay, and other cytokines with ELISA. IFN-stimulated gene signatures (ISG) were measured using qPCR. To determine whether GILZ regulates IFN in human SLE, we mined a public gene expression dataset GSE10325. Becker et al., 2013

Results: Deletion of GILZ resulted in excess pDC secretion of IFN in response to TLR7 (p=0.0012) and TLR9 (p=0.01) stimulation, and BMDC secretion of IFN, IL-6 and TNF α in response to TLR7 (p=0.0039, 0.017, 0.033), TLR7/8 (p=0.001, <0.0001, <0.0001) and TLR9 (p=0.005, <0.0001, 0.0034) stimulation respectively. Dexamethasone (DEX) induced GILZ in WT pDC and BMDC, and TLR stimulation suppressed GILZ expression in BMDC, but TLR-stimulated GILZ $^{-/-}$ cell failed to suppress IFN in response to DEX. Moreover, GILZ deficiency was associated with increased ISG in naïve spleen cells, naïve BMDCs and TLR7/9 stimulated pDC of GILZ $^{-/-}$ mice compared to WT mice. Correspondingly, increased IFN was seen in GILZ $^{-/-}$ mice in response to TLR7/8 stimulation *in vivo*. In GSE10325, we show that lower expression of GILZ was associated with high ISG (*IFI44*, *IFI44L*, *RSAD2*, *IFI27*) (p=0.0021) in SLE patient peripheral blood B cells, and GILZ mRNA was negatively correlated with IFN signature ($r=-0.63$, p=0.017) which in turn positively correlated with disease activity (SLEDAI2k) ($r=0.77$, p=0.002).

Conclusions: GILZ is an endogenous regulator of increased IFN production in response to TLR stimulation *in vitro* and in mice, and is negatively correlated with ISG in human SLE. This suggests that GILZ negatively regulates type I IFN production and GILZ based therapy may be a potential therapeutic strategy that could reduce steroid dependence in SLE.

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FRI0269 DEFICIENCY OF GLUCOCORTICOID-INDUCED LEUCINE ZIPPER (GILZ) DISINHIBITS IFN PATHWAYS AND EXACERBATES NEPHRITIS IN THE LYN-DEFICIENT MURINE MODEL OF LUPUS

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Background: Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease of unknown etiology. Lyn-deficient mice develop lupus-like autoimmunity due to hyperactive B cells resulting in excess IL-6 production, and cyclical exacerbation of inflammation by further activation of B and T cells. Tsantikos et al., 2010 C57BL/6 mice deficient in glucocorticoid-induced leucine zipper (GILZ), an intracellular protein involved in glucocorticoid effects on immunity, develop lupus-like autoimmunity and excess B cell activation. Jones et al., 2016. However, the effect of GILZ in lupus-prone mice is unknown.

Objectives: We aim to test the hypothesis that GILZ modulates autoimmunity in the lym deficient murine model of lupus.

Methods: We generated GILZ-deficient mice on a *lyn*-deficient background (GILZ-*lyn* double knock out (DKO)) and compared them to WT and *lyn*KO mice. The effects of GILZ deficiency on spleen weight, nephritis, Type I interferon-induced genes (ISG) and autoantibodies were examined.

Results: We observed heightened lupus-like autoimmunity in GILZ-lym DKO mice, compared to LynKO, that include increased spleen weights ($p=0.041$) and more severe glomerulonephritis, especially segmental necrosis. A panel of ISG (*ifih44*, *uspi8*, *oas3*, *cxcl10*, *isg15*, *mx1*, *irf7*, *stat1* and *ifih3*) and an overall ISG score was significantly increased ($p=0.0023$) in GILZ-lym DKO mice compared to LynKO. In contrast, serum autoantibodies (dsDNA, Sm, histone, Jo-1, Scl-70, SSA, SSB, U1RNP, Ro52,) were not increased in GILZ-lym DKO mice compared to LynKO mice.

Conclusions: In LynKO lupus-prone mice, spleen weight, glomerulonephritis, and ISG profiles were significantly exacerbated by GILZ deficiency, while autoantibody titres were unaffected. This suggests that endogenous GILZ exerts an inhibitory effect on IFN pathways, in this lupus model. Therefore, GILZ potentially regulates the cycle of inflammation in SLE by inhibiting IFN responses