as compared to controls. A combination of inhibitors and gene expression studies showed that glucose oxidation rather than aerobic glycolysis is a major metabolic pathway of lupus T cells. *In vitro*, both metformin and 2-DG blocked IFNγ production and metformin increased IL-2 production. *In vivo*, a combined treatment with metformin and 2-DG normalised T cell metabolism and reversed disease phenotypes in all four lupus mouse models. Remarkably, the number of $T_{FH}$ cells, which correlates with disease severity in patients, was normalised by the combination treatment in every model. Further, excessive IFNγ production by CD4 T cells from SLE patients was also normalised by metformin. Finally, $CD4^+$ T cells from lupus patients showed a metabolic signature with over-expression of genes promoting glucose utilisation, mitochondrial oxidative phosphorylation and sterol synthesis.

**Conclusions** The combination of a glucose inhibitor with metformin restores T cell function and reverses disease across diverse mouse models of SLE, and metformin treatment normalises the function of T cells from SLE patients. We propose that T cell metabolism may serve as a biomarker of disease activity and provides a novel target for immune intervention in SLE.

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## AI-26 INTESTINAL IGA AS PATHFINDERS TO IDENTIFY MICROBIOME PATHOBIONT CANDIDATES IN SLE

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**Background** SLE is an archetypical systemic autoimmune disease, which has been attributed to interactions between genetic and environmental factors that are currently not well understood. Yet recent reports have begun to elucidate how intestinal bacteria influence the development of physiologic B-cell/T-cell responses, and can affect the pathogenesis of inflammatory and autoimmune conditions. Our studies are designed to shed light on the potential roles of the gut microbiome in SLE pathogenesis.

**Methods** We have assembled and characterised a cohort of 60 female SLE patients and 20 healthy controls. DNA from the unfractionated bacteria in faecal samples, and from the sorted endogenous IgA-coated and non-coated bacterial fractions, was then extracted. 16 S bacterial rRNA genes were then barcoded and amplified, and over 20,000 reads were determined per sample using illumina NGS technology. Faecal and serum total Ig and autoantibodies were measured by ELISA.

**Results** Our analysis showed less microbiome diversity in SLE than healthy controls ($p = 0.002$). This dysbiosis was treatment independent, with more severe intestinal dysbiosis and decreased bacterial diversity in patients with high disease activity, based on SLEDAI. In addition, SLE patients had increased representation of certain bacterial families, genus's and species, based on 16 S rRNA assignments of operational taxonomic units (OTUs). Patients with active disease displayed contractions of bacterial taxa with reported protective properties and reciprocal expansions of taxa with putative pathobiont properties. We also assessed IgA, which is the most prevalent antibody isotype made by the human body, and found evidence of exuberant levels in both intestinal and blood samples of SLE patients. While only a minority of bacterial taxa are specifically coated by endogenous intestinal IgA, IgA-coated bacteria in SLE patients had differential representation with recurrent taxa-specific expansion in SLE patients. Strikingly, *Prevotella copri*, which has recently been linked to new-onset RA, was significantly over-represented among the IgA-coated taxa only in SLE patients with high disease activity, and was not detected in healthy controls.

**Conclusion** Our studies provide the first evidence that SLE is associated with gut microbiome dysbiosis with expansions of specific bacterial taxa that may contribute to immune dysregulation. This imbalance was more significant in patients with high disease activity Characterisation of in vivo IgA-coated bacteria demonstrated that certain microbes taxa/species are preferentially recognised by the adaptive immune system of SLE patients, and these differ significantly from healthy adults. We are now studying these candidate pathobionts in longitudinal studies to address whether the microbiome predicts and/or tracks flares.

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## AI-27 BACTERIAL AMYLOIDS FROM BIOFILMS BREAK TOLERANCE IN LUPUS

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**Background** Systemic lupus erythematosus (SLE) is a multifactorial autoimmune disease, in which infections are considered to play a pathogenic role, but the cellular and molecular culprits remain unknown. Bacterial biofilms are multicellular bacterial communities important in the establishment of chronic infection by pathogens. Bacteria produce amyloids, complex proteins with a conserved beta sheet structure, that strengthen the extracellular matrix of their biofilms. We have reported that bacterial and eukaryotic DNA is incorporated into curli fibres, functional bacterial amyloids present in *Salmonella* and *E. coli* biofilms. We found that curli/DNA complexes from biofilms activate conventional dendritic cells leading to production of pro-inflammatory cytokines, including Type I interferons, *in vitro* and *in vivo*, indicating that curli are a new class of danger signals. I.p. infections with curli-expressing *S.* Typhimurium or E. Coli Nissle, and also systemic administration of curli/DNA complexes purified from *Salmonella* biofilms accelerated onset in lupus-prone NZBxW/F1 mice and triggered autoantibodies production in non-predisposed mice, suggesting curli/DNA complexes as novel players in SLE pathogenesis.

**Materials and methods** In order to determine the cellular and molecular players in the acceleration of lupus by curli-expressing infections, bone marrow-derived cultures of conventional dendritic cells and macrophages were generated *in vitro* and B cells were isolated *ex vivo* from NZBxW/F1 lupus-prone mice, TLR-deficient mice and wild-type mice and stimulated with curli/DNA complexes purified from *Salmonella* biofilms. Moreover, lupus prone and control mice were infected i.p. and by oral gavage with curli-expressing or curli-deficient *S.* Typhimurium and the effects on dendritic cells, macrophages, and B cell activation, and production of autoantibodies were studied. A novel ELISA was developed to measure anti-curli antibodies in SLE patients and infected mice.

**Results** We found that Curli and DNA synergistically activate innate and adaptive immune cells, *in vitro* and *in vivo*, via TLR2 and TLR9, leading to a Type I interferon response. We found that curli/DNA complexes can directly stimulate proliferation and

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