Response to: 'The level of peripheral regulatory T cells is linked to changes in gut commensal microflora in patients with systemic lupus erythematosus' by Zhang *et al* and the phylogeny of a candidate pathobiont in lupus nephritis

We appreciate the opportunity to respond to the correspondence from Zhang *et al*,¹ and fully agree with the importance of elucidating the specific roles of individual taxa in clinical lupus pathogenesis. These authors assert that the candidate pathobiont in our earlier paper 'is lacking in a precise link with lymphocytes...'. Yet, this is completely erroneous as we showed that lupus patients with expansions of the *Ruminococcus gnavus* species also had circulating antibodies that recognised strain-restricted lipoglycan antigens in this candidate pathobiont species.² These peripheral immune responses were also shown to be cross-reactive with IgG anti-native DNA antibodies that have well-documented roles in lupus pathogenesis. Of course, circulating antibodies are produced by peripheral B cells and end-differentiated plasma cells. Indeed, the importance of this type of mechanistic link has also been demonstrated in mice colonised with the commensal *Akkermansia* species, which has some potential properties akin to our candidate pathobiont, and also has mucinolytic properties that may contribute to gut leakiness and can similarly induce systemic species-specific systemic IgG responses.³

Zhang *et al* seek to highlight their own observations regarding a direct correlation between the level of T cells in the blood, bearing a Treg phenotype, and gut abundance of the *Ruminococcus* genus, based on 16S rRNA library analysis. Direct evidence, however, of immune recognition of antigens from this taxa by peripheral Tregs is missing.

Notably, there appears to be a serious misunderstanding on the part of these authors. As stated in our paper, *R. gnavus* was originally mis-assigned within bacterial phylogeny and in fact it is neither a member of the genus *Ruminococcus* nor the family Ruminococcaceae, but is in the genus *Blautia* in the family Lachnospiraceae.^{4,5} Hence the analysis presented of their lupus cohort database of phylogenetic representation is not directly relevant to our findings. These names are unfortunately confusing, although the correct phylogenetic assignments have been sorted out.^{4,5}

Our report further explained the greater potential implications of host colonisation by *R. gnavus*² and this species has now been implicated in several inflammatory and autoimmune diseases (discussed by Silverman *et al*⁶). Moreover, the link between *R. gnavus* with lupus, a disease with a strong hallmark of B-cell abnormalities and autoantibody production, may be intimately intertwined with the local production and postulated systemic release of a recently identified *R. gnavus* outer membrane protein with the properties of a B-cell superantigen.⁷ Taken together, these findings highlight the limits of 16S rRNA based taxa assignments as greater mechanistic insights will in

part require the characterisation of *R. gnavus* strains from lupus patients with active disease.

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