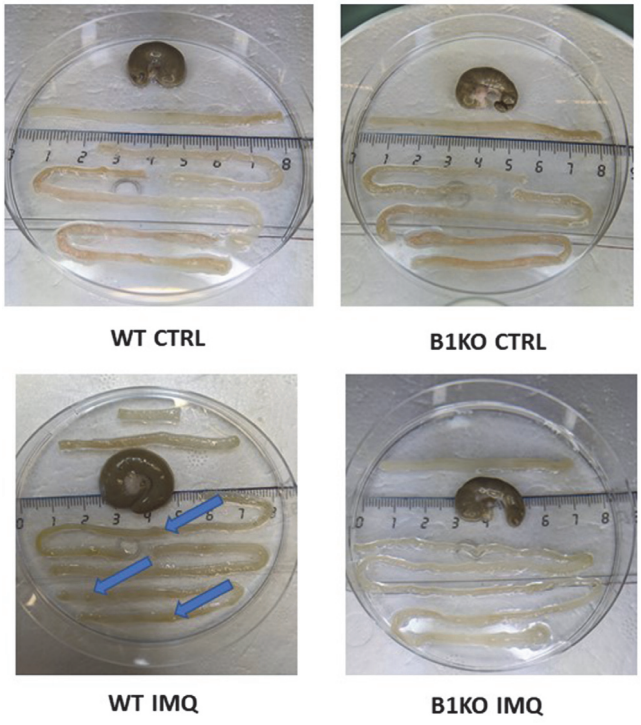
reduction in disease severity in mice. In the recent years, IL-10 producing B cells (so-called regulatory B cells) are being characterised for their immunosuppressive role in autoimmune inflammation and possible relationship with microbiota composition.

Purpose We aimed to determine the influence of the gut microbiota composition, driven by Bank1, in IL-10+ B cell induction as well as the possible role of these cells in disease severity.

Methods We have characterised the manifestations of lupus in the gut associated lymphoid tissue using an imiquimod-induced murine model of lupus (TLR7-dependent). To analyse IL-10 producing B cells, immune cells isolated from Peyer's patches of C57Bl/6 WT mice and Bank1 -/- were stimulated with PMA/Ionomycin/Monensin and analysed by flow cytometry. To study microbiota influence in IL-10 production by B cells, we used single cage mice and littermates and sequenced the V4 region of 16S RNA gene.

Results and Conclusion The imiquimod-induced murine model of lupus leads to persistent gut inflammation with changes in microbiota composition in WT and Bank1 -/- mice. In these mice, the intestinal inflammation and local immune alterations resulted in increased gut permeability and caused intestinal blockade (image 1). This affectation is similar to that observed in human SLE patients. Mice deficient for Bank1 gene experienced a milder disease and exhibited a microbiota composition that was significantly different compared with their WT counterparts (principal components analysis). More specifically, the appearance of specific species belonging to the genus Porphyromonadaceae upon the induction of an inflammatory process only in Bank1 knock-out mice were related with reduced disease severity. To determine the contribution of gut microbiota to lupus inflammation, we induced the disease in littermate mice that inherited the Bank1 KO microbiota. We observed a normalized immune response that seems to be more alike to that observed in Bank1 KO mice grown separately from their WT counterparts. We then analysed the IL-10-producing cells in the gut and found that IL-10+ B cells readily increased in Peyer's patches upon lupus inflammation in Bank1 deficient mice, but not in WT mice. When lupus was induced in littermates, the levels of IL-10+ B cells were normalized across WT and Bank1 KO mice, suggesting a possible role of microbiota in regulatory B cell induction. Further studies are, however, needed to determine whether Bank1 is required for IL-10 producing B cell activation or if its contribution is mediated by changes in the gut microbiota composition.



Abstract PO.4.91 Figure 1 Representative intestinal tracts from WT and Bank1 KO (B1KO) mice at 20 weeks of age with (IMQ) and without (CTRL) lupus induction. It can be appreciated how the inflammation in WT mice after the treatment induces an increase in the caecal size and the Peyer's patches dimension (normally not visible without microscopic magnification, pointed with arrows in the WT IMQ image). In B1KO mice, however, the caecum remains unaltered and the inflammation at Peyer's patches levels is significantly lower than that achived by WT mice. Representation of three different experiments with 3–5 mice per group each experiment

PO.4.92 TAXONOMY, TREATMENT, TARGETS AND REMISSION IN SYSTEMIC LUPUS ERYTHEMATOSUS: THE 3TR-SLE STUDY PROTOCOL

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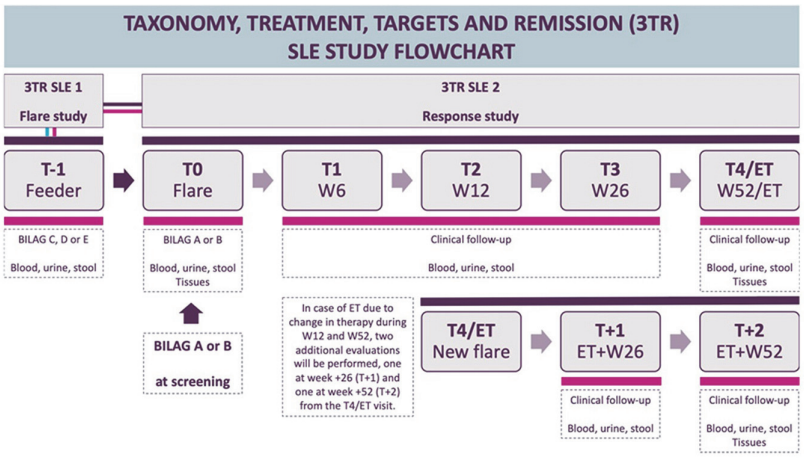
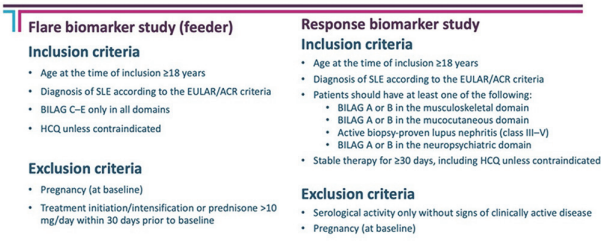
Purpose Taxonomy, Treatment, Targets and Remission (3TR) is a transdisciplinary consortium funded by the Innovative Medicine Initiative (IMI) and European Federation of Pharmaceutical Industries and Associations (EFPIA), aimed at performing a longitudinal multi-dimensional molecular analysis in patients with autoimmune, allergic, and inflammatory diseases. The main hypothesis of the 3TR project is that data obtained from multilevel omics analysis across seven different diseases will identify shared biological pathways that better predict response or non-response to therapies despite their differences in terms of clinical phenotypes and pathogenetic mechanisms. Systemic lupus erythematosus (SLE), rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, asthma, and chronic obstructive pulmonary disease are the chronic disorders that will be investigated for shared biomolecular pathways.

Methods Centralised and standardised clinical data and sample collections will be a resource for studies and knowledge. Patients from multiple European centers are recruited for a longitudinal clinical follow-up and collections of blood, urine, stools, saliva, and relevant tissue samples at multiple timepoints. Among other analyses, we plan to perform transcriptome profiling in blood and tissues, including single-cell



Abstract PO.4.92 Figure 1 Thr 3TR-SLE study flowchart

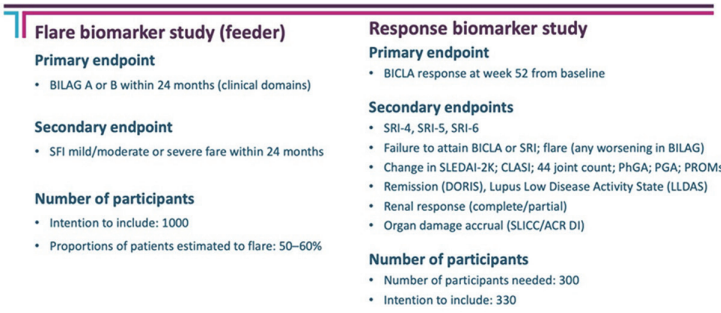


Abstract PO.4.92 Figure 2 Inclusion and exclusion criteria

analyses, as well as analysis of the metabolome, microbiome, and lipid mediators in urine and stools. Data will be available and integrated through highly innovative bioinformatics analysis platforms.

Results For SLE, two observational prospective studies have been designed: (i) the flare biomarker study (3TR-SLE 1), and (ii) the response biomarker study (3TR-SLE 2). In 3TR-SLE 1, patients with quiescent SLE (no BILAG A or B) are recruited from ~25 European tertiary referral centres and are followed up until they develop a flare, or for a maximum of 24 months. Clinical assessments and sampling are conducted at baseline and at flare, or at 24 months if no flare occurs. Patients who develop a flare (BILAG A or B resulting in a change in therapy) are asked to participate in 3TR-SLE 2, where assessments and sampling occur on 5 occasions through 52 weeks (baseline and week 6, 12, 26, 52). Patients at flare during screening are directly recruited in 3TR-SLE 2. Patients who develop flares during follow-up after an initial response are assessed and sampled at 2 additional timepoints (26 and 52 weeks post-flare). The 3TR-SLE study flowchart and inclusion and exclusion criteria are detailed in the figures. We intend to include 1000 patients with SLE in 3TR-SLE 1, and 330 in 3TR-SLE 2.

Conclusions Several innovations are expected within the 3TR project towards increased knowledge of pathogenetic mechanisms underlying clinical SLE phenotypes, and towards unraveling the complexity of the SLE biomolecular heterogeneity, the pathways of response or non-response to treatment, and the processes leading up to disease flare. Insights from studies within SLE and across 3TR diseases will facilitate evidence-based counselling and prevention, drug repurposing, personalised decision-making, and improved long-term prognosis for people living with SLE.



Abstract PO.4.92 Figure 3 Primary and secondary endpoints