the treatment of multiple autoimmune and inflammatory diseases, particularly B cell- and/or autoantibody-related diseases such as SLE, Sjögren's syndrome, and other connective tissue diseases. A Phase 1 study of ALPN-303 in adult healthy volunteers (NCT02033448) is ongoing. REFERENCES:


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Sjögren’s Disease and Systemic Lupus Erythematosus DDX6-CXCR5 Risk Intervals Reveal Common SNPs with Functional Significance in Immune and Salivary Gland Cells

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Background: Sjögren’s Disease (SjD) and Systemic Lupus Erythematosus (SLE) are autoimmune diseases with several shared characteristics and similar genome-wide significant associations with the DDX6-CXCR5 locus. DDX6 suppresses interferon-stimulated gene expression and CXCR5 regulates T cell functions in immunomodulation. Objectives: To identify and characterize functional SNPs in the DDX6-CXCR5 interval. Methods: ImmunoChip data from European populations (3785 SLE cases; 1916 SjD cases; 6893 controls) were imputed and SNP-trait associations tested. Bayesian statistics defined a credible SNP set that was refined using bioinformatic analyses (RegulomeDB, Haploreg, ENCODE, promoter capture Hi-C, eQTLs, etc.). Electrophoretic mobility shift assays (EMSAs) and luciferase expression assays were used to test allele-specific SNP function in EBV-transformed B (B. Jurkidjian), D (D. Koene, D. R. Koch) and T cell lines and promoter activity in T cells (p<0.01). Risk allele of rs4938573 in the promoter/enhancer region of DDX6 and CXCR5. EMSAs and luciferase experiments showed cell-type-specific differences in protein binding and promoter or enhancer activity, respectively, at each SNP. Risk allele of rs57494551 increased enhancer activity in B cells and A253 cells (p<0.001), but decreased promoter activity in T cells and A253 cells (p<0.01). SNP rs4938572 is an eQTL of DDX6 in T cells, and the risk allele significantly increased protein binding, promoter and enhancer activity in T cells (p<0.01). Risk allele of rs4938572 also increased promoter activity in A253 cells (p<0.01), but had no effect on promoter or enhancer activity in B cells. SNP rs4936443 showed no promoter or enhancer activity in immune cells, but the risk allele showed
significant promoter and enhancer (p<0.001) activity in A253 cells. SNP rs71712781 showed decreased enhancer activity in EBV B cells, T cells, and A253 cells (p<0.05) and increased promoter activity in A253 cells (p<0.001). SNP rs49385731 showed decreased promoter activity in EBV B cells, T cells, and A253 cells (p<0.05), decreased promoter activity in EBV B cells (p<0.05), and increased enhancer activity in A253 cells (p<0.0001). Overall, A253 cells exhibited more allele-specific effects on promoter and enhancer activity across the five SNPs compared to tested immune cells. In addition to DDX6 and CXCIR5, rs57494551 and/or rs49385712 are reported eQTLs for several other genes of interest in the local chromatin regulatory network: IL10RA in T cells, TRAPPC4 in salivary gland and activated macrophages, and long non-coding (Inc)RNA AP002954.1 in T cells and whole blood. 3C-qPCR in EBV B and A253 cells showed that the two regulatory regions carrying rs4938572 or rs57494551 interacted with a region upstream of DDX6 that includes AP002954.1. Hi-C data showed looping between AP002954.1 and the regulatory region carrying rs4938572 and rs57494551 in T cells.

Conclusion: SJ and SLE share similar genomic architecture across the DDX6-CXCIR5 risk interval with several common SNPs showing immune and salivary gland type-specific allele effects on protein binding and/or enhancer/promoter activity. Extensive bioinformatic analyses suggest that the SNPs likely work within the local chromatin regulatory network to regulate cell type-specific expression of several genes on the interval. Ongoing studies will use 3C-qPCR to assess allele-specific chromatin interactions between the SNPs and these genes in different cell types, and CRISPR to determine how the risk alleles alters expression.

Disclosure of Interests: Mandi M Wiley: None declared, Bhuvan Khatri: None declared, Kandice L Tesseneer: None declared, Michelle L Joachims: None declared, Anna M Stolarczyk: None declared, Anna Nagel: None declared, Astrid Rasmussen: None declared, Simon J. Bowman Consultant of: Abbvie, Galapagos, and Novartis in 2020-2021, Lida Radfar: None declared, Roaiid Omdal: None declared, Marie Wahren-Herlenius: None declared, Blake M Warner: None declared, Torsten Witte: None declared, Roland Jonsson: None declared, Mau- reen Rischmueller: None declared, Patrick M Gaffney: None declared, Judith A. James: None declared, Lars Ronnblom: None declared, R Hal Sc Sofield: None declared, Xavier Mariette: None declared, Wan Fai Ng: None declared, Kathy Sivils Employee of: current employee of Janssen., Gunnar Nordmark: None declared, Marie Wahren-Herlenius: None declared, Blake M Warner: None declared, Rasmus Rasmussen: None declared, Simon J. Bowman Consultant of: Abbvie, Galapagos, and Novartis in 2020-2021, Lida Radfar: None declared, Roaiid Omdal: None declared, Marie Wahren-Herlenius: None declared, Blake M Warner: None declared, Torsten Witte: None declared, Roland Jonsson: None declared, Mau- reen Rischmueller: None declared, Patrick M Gaffney: None declared, Judith A. James: None declared, Lars Ronnblom: None declared, R Hal Sc Sofield: None declared, Xavier Mariette: None declared, Wan Fai Ng: None declared, Kathy Sivils Employee of: current employee of Janssen., Gunnar Nordmark: None declared, Betty Tsao: None declared, Christopher Lessard: None declared.