herpes simplex virus 1 infection in Kyoto Encyclopedia of Genes and Genomes pathways. Especially, FCGR1A, IRF7, OAS2, CAMP, MX1, OAS3, OAS1, DEFA3, ISG15, and RSAD2 were involved in virus mediated SLE mechanism, and the expression for OAS1, OAS2, and IRF7 was closely associated with the quantities of colony forming unit-monocyte and colony forming unit-granulocyte.

Conclusion: Identifying virus mediated SLE genes and quantifies of immune cells were used to understand the pathological process and perform early diagnosis of SLE, and will lead to clinical tools for treating SLEs in patients.

REFERENCES:

[1] Ghodke-Puranik Y and Niewold TB. Immunogenetics of systemic lupus erythematosus: A comprehensive review. J Autoimmun 2015; 64: 125-136.

[2] Teruel M and Alarcón-Riquelme ME. The genetic basis of systemic lupus erythematosus: What are the risk factors and what have we learned. J Autoimmun 2016; 74: 161-175.

[3] Lauwerys BR, Hachulla E, Spertini F, et al. Down-regulation of interferon signature in systemic lupus erythematosus patients by active immunization with interferon alpha-kinoid. Arthritis Rheum 2013; 65: 447-456.

[4] Frishberg A, Brodt A, Steuerman Y and Gat-Viks I. ImmQuant: a user-friendly tool for inferring immune cell-type composition from gene-expression data. Bioinformatics 2016; 32: 3842-3843.

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Adaptive immunity (T cells and B cells) in rheumatic diseases

POS0397 SSD6453, A NOVEL AND HIGHLY SELECTIVE BTK/JAK3 DUAL INHIBITOR IS EFFICACIOUS IN MULTIPLE PRE-CLINICAL MODELS OF INFLAMMATION

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Background: The mechanism of inflammatory diseases is complicated and dysfunction of multiple immune cells is thought to be directly related to the pathogenesis. Targeting either JAK-STAT or BCR signaling has been proved solid clinical efficacy in multiple inflammatory diseases, such as rheumatoid arthritis (RA) and multiple sclerosis (MS). And the combination of BTK and JAK inhibitors demonstrated synergistic effects for the treatment of inflammation models in pre-clinic. JAK3 expression is largely restricted to leukocytes and involves functions in JAK1/JAK3 heterodimer in signal transduction, it might be a more effective and safer target. Meanwhile, both BTK and JAK3 possess a cysteine residue in their active site and this feature makes it possible to design a dual inhibitor. SSD6453 is a highly selective and irreversible JAK3/BTK dual inhibitor which may have synergistic effects for the treatment of RA and other inflammatory diseases such as MS.

Objectives: To develop a potent, oral, highly selective JAK3/BTK inhibitor for treatment of multiple inflammatory diseases.

Methods: ADP-GLO based biochemical assays were performed to determine the enzymatic inhibitory effect and selectivity for JAK family. The target engagement was evaluated by IgM induced pBTK and IL-2 induced pSTAT5 in human PBMCs. In vivo efficacy was evaluated by rat collagen-induced arthritic (CIA) model and mice experimental autoimmune encephalomyelitis (EAE) models induced by MOG1-125 or MOG35-55, respectively. BTK occupancy in spleens post last dose 24h and IL-2 induced pSTAT5 in whole blood post last dose 0.5h were used to evaluate targets inhibitions. Osteoclast was stained by IHC in pathological section of rat paws.

Results: In biochemical assays, SSD6453 inhibited BTK and JAK3 with the IC_{50} values of 3.4 nM and 1.1 nM, respectively. Notably, SSD6453 displayed high selectivity against JAK1 (510 fold), JAK2 (75 fold) and TYK2 (525 fold). In cellular assays, SSD6453 inhibited anti-IgM induced pBTK and IL-2 induced pSTAT5 in human PBMCs with the IC_{50} values of 18.8 nM and 168.8 nM, respectively. SSD6453 demonstrated favorable PK properties in broad pre-clinical species. Single oral administration of SSD6453 in rat or mouse, resulted in dose-dependent inhibition of BTK and JAKs concurrently. In the rat CIA model in which disease development was accompanied by a robust T-cell and B-cell inflammation response to collagen, SSD6453 dose-dependently inhibited paw edema. And SSD6453 at 10mpk achieved complete (95%) BTK occupancy and JAK3 inhibition and superior efficacy in comparison of tofacitinib (JAK@10 mpk) or evobrutinib (BTK @30mpk) alone, suggesting that concurrent inhibition of JAK3 and BTK lead to synergistic anti-inflammation effects. In addition, ED-1+ osteoclast count decrease was observed in paws, suggesting the prevention of SSD6453 in joint destruction. In two EAE models either induced by MOG1-125 or MOG35-55, which represented T or B dominant inflammation model, respectively, SSD6453 robustly ameliorated disease in both two models. In comparison, BTK inhibitor is efficacious only in the MOG1-125 induced model.

Conclusion: SSD6453 is a novel and high selective BTK/JAK3 dual inhibitor, and demonstrated synergistic efficacy in multiple pre-clinic inflammation models. SSD6453 showed good pharmacokinetic characteristics and well-tolerant in multiple pre-clinical species, and is moving to IND in 2022.

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POS0398 IDENTIFICATION OF THE HLA-B*51:01 IMMUNOPEPTIDOME IN BEHÇET'S DISEASE

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Background: Immunopeptidomes are peptides, bound to human leukocyte antigens (HLA), that play a key role in immune responses. HLA-B*51:01 is an HLA allele associated with Behçet's disease (BD)[1]. However, the characteristics and the role of HLA-B*51:01 immunopeptidome are not revealed in Behçet's disease.

Objectives: To investigate the difference of HLA-B*51:01 immunopeptidome between Behçet's disease and healthy controls (HCs) and to select candidate peptides which have a pathogenic role in Behçet's disease.

Methods: HLA-bound peptide profiles were established through analysis of plasma samples from HLA-B*51:01–positive BD patients and HCs. HLA-class I molecules were immunoprecipitated, and liquid chromatography-tandem mass spectrometry (LC-MS/MS) was performed. Then, HLA-B*51:01–binding peptides were assessed in terms of binding affinity using NetMHCpan. Finally, the

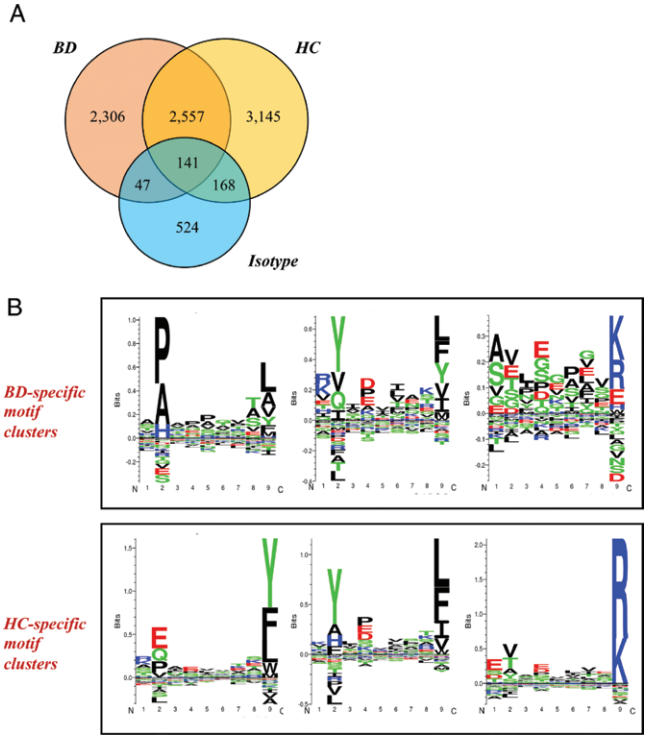

Figure 1. Venn diagram of the identified 8–13-mer peptides and graphs showing the motif clusters. (A) Venn diagram showing the numbers of peptides detected by immunoprecipitation with BD patients or HCs. The number of peptides isolated with isotype antibodies were also depicted. (B) Motif clusters of human leukocyte antigen (HLA)-B*51:01-positive BD patients and HCs.

immunological characteristics of selected peptides were analyzed in BD patients and HCs, using ELISpot, flow cytometry, and dextramer staining.
Results: 2,306 peptides were present only in BD patients, while 3,145 peptides were detected only in HCs. Immunopeptidome of BD patients preferentially showed hydrophobic amino acids at amino acid position 2 (Figure 1). Ten peptides were selected which were confirmed to be preferentially expressed in BD patients compared with HCs. When bound to HLA-B*51:01 in monocyte-derived dendritic cells (Mo-DCs) or peripheral blood mononuclear cells, these peptides activated T cells and induced surface expression of CD69 and CD107, as well as the secretion of inflammatory cytokines such as interferon (IFN)-γ and tumor necrosis factor (TNF)-α.
Conclusion: HLA-B*51:01 immunopeptidome can play a critical role in the development of BD by activating T cells and inducing the secretion of inflammatory cytokines.
REFERENCES:
[1] Takeuchi M, Mizuki N, Meguro A, Ombrello MJ, Kirino Y, Satorius C, *et al.* Dense genotyping of immune-related loci implicates host responses to microbial exposure in Behcet's disease susceptibility. *Nat Genet* **49**, 438-443 (2017).
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POS0399 CHARACTERIZATION OF HSP60, A STROMAL-DERIVED AUTOANTIGEN, RECOGNIZED BY RA SYNOVIAL RECOMBINANT MONOCLONAL ANTIBODIES

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Background: Up to 50% of rheumatoid arthritis (RA) patients display synovial ectopic lymphoid structures (ELS) supporting B-cell autoreactivity toward locally generated citrullinated and other translationally modified antigens. Recently, screening a large number of recombinant monoclonal antibodies (rmAbs, n=71) which we derived from locally differentiated B-cells from RA ELS+ synovium [1], we identified a subset of antibodies which specifically recognise fibroblast-like-synoviocytes (FLS) (10 out of 71), suggesting FLS as a cellular source of autoantigens fuelling the local autoimmune response. We reported that calreticulin is one of the antigenic targets of these anti-FLS rmAbs, while the nature of other FLS-derived autoantigens is still unclear [2].
Objectives: Here we aimed to define other stromal-derived autoantigens from RA-FLS targeted by RA-rmAbs.
Methods: Western blotting/mass-spectrometry were used to identify potential autoantigens from RA-FLS protein extracts. Putative candidates were validated using colocalization immunofluorescence confocal microscopy/ELISA/immunoprecipitation assay. Finally, both serum and synovial fluid (SF) from RA patients (OA patients used as control) were tested for immunoreactivity towards the putative antigen.
Results: Following immunoprecipitation and mass-spectrometry analysis, among the anti-FLS antibodies we identified a subset of RA-rmAbs which display strong reactivity towards heat shock protein 60 (HSP60). Three RA-rmAbs confirmed a clear immunoreactivity towards HSP60 in ELISA assay in a dose-dependent manner. Confocal microscopy did not show co-localization between anti-HSP60 RA-rmAbs and HSP60, suggesting that HSP60 act as autoantigen when released from the RA-FLS in stress condition. Finally, anti-HSP60 Abs were preferentially detected in RA-SF versus OA-SF, with an accumulation of HSP60 in RA-SF versus RA sera.
Conclusion: Here, we identified synovial B cell-derived RA-rmAbs locally differentiated within the ELS+ RA synovium reacting toward HSP60, suggesting that FLS-derived HSP60 may contribute to fuel the local autoimmune response. Elucidating the mechanisms involved in RA-FLS activation *in vitro/in vivo* will be important to clarify the anti-FLS rmAbs functional role in modulating inflammation.
REFERENCES:
[1] Corsiero *et al*, ARD 2016; [2] Corsiero *et al*, JI 2018.
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POS0400 MODULATION OF HUMAN EARLY B CELL DEVELOPMENT THROUGH TARGETED DEGRADATION OF IKAROS AND AIOLOS WITH IBERDOMIDE

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Background: B differentiation in the bone marrow (BM) is impaired in patients carrying mutation in the IKFZ1 gene, coding for Ikaros a zinc-finger transcription factor. High Ikaros expression is on the contrary associated with systemic lupus erythematosus[1] and multiple myeloma[2]. Targeted treatment with iberdomide, a cereblon modulator which enhances degradation of Ikaros and Aiolos, is under clinical investigation in multiple myeloma patients and systemic lupus erythematosus. However, consequences of the treatment on human early B cell development remain elusive. Immature B cells develop in the BM from hematopoietic stem cells. An intricate network of transcription factors regulates the maturation process. Ikaros and Aiolos regulate gene expression during B cell development. As reported in mice, Ikaros is essential for the commitment to the lymphoid lineage and later, together with Aiolos, ensures the transition from pre-BII large to pre-BII small cells.
Objectives: Investigate the effect of iberdomide (CC-220) on human early B cell development simulated in vitro.
Methods: We tested the impact of iberdomide on short term culture of BM-derived lymphocytes and in a unique in vitro modeling of early B cell development starting from cord blood (CB)- CD34+ progenitors [3, 4]. We used multi-dimensional spectra flow cytometry (17-color pan-el) to dissect early B cell subpopulations.
Results: Iberdomide treatment led to enhanced degradation of Ikaros and Aiolos in both BM- and CB-derived cultures. Addition of iberdomide early (day 7) to the CB-derived culture impaired the specification to the lymphoid lineage and later also the commitment to the B cell lineage. These observations were confirmed by reduced E2A and PAX5 gene expression, respectively. Treatment with iberdomide on B cell precursors (pro- and pre-B cells, day 28 of culture) on one side it enhanced the proliferation of early progenitors resulting in increased amount of CD10+CD38+ lymphoid-committed cells. On the other side, it resulted in a accumulation of pre-B cells and inefficient development of immature B cells.
Conclusion: Iberdomide impairs the commitment to the lymphoid lineage by enhancing Ikaros' degrada-tion. When targeting already committed B cells, iberdomide treatment undermines the transition of pre-BII large to pre-BII small cells due to increased Aiolos' degradation, conse-quently impairing the development of immature B cells. Our data can instruct immunologi-cal monitoring of patients treated with iberdomide, and provide insights in the mechanisms of therapeutic efficacy.
REFERENCES:
[1] Rivellese, F., et al., Effects of targeting the transcription factors Ikaros and Aiolos on B cell activation and differentiation in systemic lupus erythematosus. Lupus Sci Med, 2021. 8(1).
[2] Thakurta, A., et al., Developing next generation immunomodulatory drugs and their combinations in multiple myeloma. Oncotarget, 2021. 12(15): p. 1555-1563.
[3] Kraus, H., et al., A Feeder-Free Differentiation System Identifies Autonomously Proliferating B Cell Precursors in Human Bone Marrow. The Journal of Immunology, 2014. 192(3): p. 1044-1054.
[4] Troilo, A., et al., Nonpermissive bone marrow environment impairs early B-cell development in common variable immunodeficiency. Blood, 2020. 135(17): p. 1452-1457.
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POS0401 SERUM ANTIBODIES TO TYPE I COLLAGEN IN PERIPHERAL ARTHROPATHY ASSOCIATED WITH INFLAMMATORY BOWEL DISEASE

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Background: Immunological disorders play an important role in the pathogenesis of inflammatory bowel disease (IBD). Type I collagen (COL1) is the main component of the intercellular matrix of connective tissue. It can be assumed that the immune disorders leading to the production of autoantibodies to collagen play a role in the pathogenesis of arthropathy associated with IBD.
Objectives: to study the level of IgM and IgG to type I collagen (COL1) in peripheral arthropathy associated with IBD.