herpes simplex virus 1 infection in Kyoto Encyclopedia of Genes and Genomes pathways. Especially, FCGR1A, IRF7, OAS2, CAMP, MX1, OAS3, OAS1, DEF3, ISG15, and RASD2 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 quantities 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

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

POS0397
SSD6453, A NOVEL AND HIGHLY SELECTIVE BTK/JAK 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 BTK/JAK 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 whole blood post last dose. The enzymatic inhibitory effect and selectivity for JAK family. The target engagement was evaluated by IgM induced pBTK and IL-2 induced pSTAT5 in whole blood post last dose 0.5h and IL-2 induced pSTAT5 in whole blood 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 IC50 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 IC50 values of 18.8 nM and 168.6 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+ 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-clinic models, and is moving to IND in 2022.

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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.