Table 1. Tcell subsets in Rheumatoid Arthritis and Osteoarthritis.

CD4 subtype	RA		OA	
	PB	SF	PB	SF
	N=80	N=30	N=30	N=30
Th1	26.65 ± 5.59	34.99 ± 1.30	25.97 ± 7.24	26.45 ± 1.87*
Th2	5.19 ± 1.9	16.36 ± 1.73	5.24 ± 2.15	1.44 ± 0.10*
Th17	14.05 ± 3.29	21.18 ± 2.04	10.81 ± 2.78*	2.45 ± 0.23*
Treg	10.68 ± 2.47	12.53 ± 2.10	11.162.95	13.04 ± 2.57

*P<0.05

Conclusion: Tregs in RA may be converted to Th1 and Th17 phenotype on exposure to inflammatory cytokine in the synovial fluid, thus losing their regulatory functions. Understanding factors influencing stability of Treg cells may help improve future therapeutics.

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Fig1: A. Comparison of plasma cytokine levels between of RA and OA patients; B. Comparison of synovial fluid cytokine levels between RA and OA patients; C. Surface characterization of in-vitro cultured Peripheral blood Treg cells of RA patients. C1 & C2 CXCR3(Th1) and CXCR6(Th17) chemokines expressing Treg cells isolated from peripheral compartment of RA patients; C3 & C4 CXCR3(Th1) and CXCR6(Th17) chemokines expressing Treg cells cultured in autologous synovial fluid. D. Comparison of expression of transcription factors in peripheral blood Treg cells of RA and OA patients: cultured with autologous synovial fluid. Expression of (D1) T-bet, (D2) ROR-g, (D3,D4) Foxp3. Mann-Whitney U test was used to analyze cytokine data, unpaired student t-test was used to analyze Treg frequency data. Paired t-test was used to analyze gene expression data. * P Value < 0.05 considered significant

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AB0095

PRECLINICAL CHARACTERIZATION OF CJ-15314, A HIGHLY SELECTIVE JAK1 INHIBITOR, FOR THE TREATMENT OF AUTOIMMUNE DISEASES

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Background: Janus kinases (JAK1, JAK2, JAK3, and TYK2) play critical roles in mediating various cytokine signaling, and has been developed as a target for autoimmune diseases such as RA. Tofacitinib, oral Pan-JAK inhibitor, demonstrated efficacy in RA patients, but its widespread use is limited by safety issues. Baricitinib, JAK1/2 inhibitor, is also known to interfere with the hematopoiesis system, such as anemia and thrombocytopenia associated with suppression of JAK2 signals. Therefore, it is necessary to develop a new potent compound that selectively inhibits JAK1 over JAK2, 3

Objectives: To identify the pharmacological characteristic based on efficacy of CJ-15314 as potent and selective JAK1 inhibitor for treatment of autoimmune disease.

Methods: In vitro, cell-based, kinase panel, Kd value and human whole blood assay were performed to determine the inhibition potency and selectivity for JAK subfamily kinases. In vivo therapeutic potential was evaluated by RA model including rat Adjuvant-Induced Arthritis (AIA) and collagen-induced arthritic (CIA). To confirm the possibility of further expansion into the autoimmune disease, BioMAP® Diversity PLUS® Panel was performed by discoverX.

Results: In vitro assay, CJ-15314 inhibited JAK kinase family in a concentration-dependent manner with IC50 values of 3.8 nM against JAK1, Selectivity for

JAK1 over JAK2, 3 was approximately 18, 83 fold greater for CJ-15314. In 1mM ATP condition, CJ-15314 has been confirmed to have the highest JAK1 selectivity over competing drugs, under 1mM ATP condition that reflects the physiological environment in the body. Similarly, Kd values has also confirmed the selectivity of JAK1, which is 10 fold higher than JAK2, 3. Accordingly, in human whole blood assays, CJ-15314 is 11 fold more potent against IL-6 induced pSTAT1 inhibition through JAK1 (IC50 value: 70 nM) than GM-CSF-induced pSTAT5 inhibition (JAK2) whereas baricitinib and filgotinib exhibited only 2 fold and 7 fold respectively.

In vivo efficacy model, CJ-15314 inhibited disease severity scores in a dose dependent manner. In the rat AIA model, CJ-15314 at 30mg/kg dose showed 95.3% decrease in arthritis activity score, 51.2% in filgotinib at 30 mg/kg, 97.7% showed baricitinib at 10 mg/kg. CJ-15314 showed superior anti-arthritis efficacy than filgotinib. CJ-15314 also minimally affected anemia-related parameters but not bicitinib end of the 2-week treatment. In the rat CIA model, like 10 mg/kg of bicitinib, 30 mg/kg of CJ-15314 also has a similar effect, with a significant reduction in histopathological scores.

In biomap diversity panel, CJ-15314 inhibited the expression of genes such as MCP-1, VCAM-1, IP-10, IL-8, IL-1, sTNF-α and HLA-DR confirming the possibility of expansion into other diseases beyond arthritis.

Conclusion: CJ-15314 is a highly selective JAK1 inhibitor, demonstrates robust efficacy in RA animal model and is good candidate for further development for inflammatory diseases.

* CJ-15314 is currently conducting a phase I trial in south Korea.

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AB0096

FCER1G GENE METHYLATION AND MIR-106/MIR-17 AS A NEW POTENTIAL EPIGENETIC MARKERS IN RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease that leads to joints destruction. One of the most important cytokine responsible for this process is interleukin 6 (IL-6). Fc receptor gamma chain (FcRγ), encoded by *FCER1G* gene, is responsible for neutrophils activation, phagocytosis, cell surface signaling pathway as well as IL-4, IL-6, IL-10 and tumor necrosis factor production. Epigenetic factors, including DNA methylation and micro-RNAs (miRs) expression regulate the genes expression on transcriptional and post-transcriptional mechanisms. There are miRs responsible for cytokines production, for example GU rich miRs, miR-106b and miR-155 were reported as associated with IL-6 overproduction.

Objectives: The aim of our study was to evaluate *FCER1G* gene methylation and miR-17 family members as epigenetic markers associated with RA, disease activity and IL-6 expression.

Methods: Bioinformatics analysis were applied to select the miRs with a possible target sites in a promoter region of *FCER1G* gene. The MiR-17 family members, including miR-17, miR-93 and miR-106b were selected for investigation. A total of 74 individuals, 50 RA patients, 84% female, aged 53.7±12.3 years (mean±SD) and 24 healthy controls (HC), 87.5% female, aged 53±8.49 years were enrolled. RA patients were selected based on DAS-28 scoring. RA patients with high disease activity (DAS28 >5.1; 58%) and remission (≤2.6; 42%) were included in the analysis. DNA was extracted from a whole blood and miRs were extracted from plasma. Quantitative real-time PCR was used for analyze both methylation and expression levels. In a randomly selected samples (16 from high