POS0838 AGOMELATINE IDENTIFIED FROM THE FDA-APPROVED DRUG LIBRARY IS THERAPEUTIC AGAINST COLLAGEN INDUCED ARTHRITIS

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Background: Treatment effect of tumor necrosis factor α (TNFα) inhibitors is still low in patients with rheumatoid arthritis (RA), around 50%-70%. Thus more drugs by targeting proliferation of synovial fibroblasts (FLS) and TNFα induced inflammatory cytokine production are needed. Repurposed use of drugs that have been used in clinic is a quick and cost-effective way to find new drugs.

Objectives: This study aims to screen drugs that could inhibit the proliferation and inflammation induced by TNFα in FLS from FDA approved on market drug library, then to assess the treatment effect of the identified drugs on collagen-induced arthritis (CIA) mouse model.

Methods: CCK8 assay was performed to screen the drugs that could inhibit FLS proliferation, followed by qRT-PCR and ELISA to select the drugs that could suppress TNFα induced inflammatory cytokine production. Then, treatment effects of the identified drugs were assessed in CIA mouse model.

Results: The first and second round drug library screening aimed to select out the drugs that could inhibit the proliferation of FLS. Results showed, from 1815 drugs, 372 drugs were indentified at the initial screening (Figure 1A) and 121 drugs were identified from the second screening (Figure 1B). The second round screening. The drugs could inhibit more than 10% absorbance at 450nm, under the red lines, were the target ones, n=121. (C-F) The third round screening. (C-D) mRNA expression levels of IL-6 and IL-8. (E-F) the secretion levels of IL-6 and IL-8. (G-H) The confirmation of drugs inhibitory effect on the inflammation cytokine production. Red asterisk indicated the comparison between TNFα group and DMSO group and blue pound signs suggested the comparison between drugs and TNFα group. (G-H) the mRNA expression levels of IL-6 and IL-8. (I-J) the secretion levels of IL-6 and IL-8. (K-L) the pathological score of inflammation and bone erosion at both the knee and the ankle after treatment with tofacitinib in CIA mouse model.

Conclusion: AGomelatine indentified from the FDA approved drug library could inhibit FLS proliferation and TNFα induced inflammation, and was therapeutic against CIA mouse model.