**Additional file 1: Figure S1.** Optimal fargesin dose screening in CIOA mice. (A) Drug treatment was administered at each stage. 10-week-old mice were subjected to CIOA and treated with vehicle or fargesin. (B) Safranin O and Fast Green staining sagittal views of tibial medial cartilage 3 weeks after intra-articular injection collagenase: sham, CIOA treated with vehicle, CIOA treated with 5, 10, and 20 mg/kg fargesin. Scale bar: 100 µm. (C and D) OARSI score was evaluated in CIOA mice treated with vehicle or fargesin in both tibia and femoral (0-12).

**Additional file 2: Figure S2.** Fargesin effects on cell viability in ATDC5 and Raw264.7 cells. (A and B) Cells were cultured with various concentrations of fargesin (0-80 µM) for 24 h and then evaluated using Cell Counting Kit-8 assay. (C) Raw264.7 cells were co-cultured with IL-4 (20 ng/mL) and various concentrations of fargesin (0-40 µM) for 24 h and then evaluated using Cell Counting Kit-8 assay.OD, optical density (n=3).

**Additional file 3: Figure S3.** Fargesin acts as a potent polarizer towards M2 macrophages in THP-1 cells. (A–C) Quantitative PCR analysis of iNOS, IL-6, and CD206 in THP-1 cells treated with LPS or IL-4 and co-treated with vehicle or fargesin (n=3).

**Additional file 4: Figure S4.** Fargesin attenuates p-S6, Rspo2 and β-catenin expression in synovium tissue of CIOA mice. (A-F) Immunostaining and quantitative analysis of cells positive for F4/80, p-S6 (A and B), Rspo2 (C and D), and β-catenin (E and F) in CIOA mice treated with vehicle or fargesin 3 weeks after intra-articular injection of collagenase. Scale bar: 50 µm. Higher magniﬁcation is shown on the right top. Scale bar: 100 µm. AC, articular cartilage; MM, medial meniscus.

**Additional file 5: Figure S5.** No significant improvement is observed in vehicle treatment compared with saline treatment 3 weeks after intra-articular injection of collagenase. (A) Cartilage degradation assessed by Safranin O and Fast Green staining. Dotted lines represent tide line. Scale bar: 50 µm (top). (B) OARSI score was evaluated in CIOA mice treated with saline or vehicle. (C-F) Immunostaining and quantitative analysis of cells positive for CD206 (C and D) and iNOS (E and F) in CIOA mice treated with saline or vehicle 3 weeks after intra-articular injection of collagenase. Scale bar: 50 µm. Scale bar: 25 µm. AC, articular cartilage; MM, medial meniscus. (n=3)