**Supplementary material**

## Supplementary methods

### Complete Freund adjuvant (CFA)-induced inflammatory arthritis model

Inflammatory arthritis model was established through i.a. injection of CFA (1 mg/ml; 5 µl; Sigma, St Louis, MO) into right hind ankle joint of mice under isoflurane (30% vol/vol) anesthesia. Nocifensive behaviors and joint swelling were evaluated over a 2- week period.

### Flow cytometry

On day 1 after gout induction, synovial tissues were collected from mouse knees and placed in cold RPMI 1640 medium containing 0.15 mg/mL Hyalauronidase (Sigma, St Louis, MO), 1 mg/mL Collagenase type IA (Sigma, St Louis, MO), and 1 mg/mL Collagenase VIII (Sigma, St Louis, MO) followed by incubation at 37°C for 1 hour. After digestion, synovial tissues were filtered with a 70 µm cell strainer, centrifuged and washed with 0.5% BSA in PBS. For LAD2 cells or PDMCs, cells were centrifuged at 300 g for 5 min and resuspended in 0.5% BSA in PBS. Cells were incubated with CD16/CD32 Fc block (1:100; eBioscience, Santa Clara, CA) for 10 min before the addition of specific antibodies. All antibodies used in this experiment were listed in Table S1. Non-viable cells were excluded by staining with 7-Aminoactinomycin D (7-AAD; 1:100; BD Pharmingen, San Diego, CA). Samples were captured with a CytoFLEX LX flow cytometer (Beckman Coulter, Indianapolis, IN). Data analysis was performed using CytExpert 2.3 (Beckman Coulter, Indianapolis, IN) or FlowJo™ 10 software (TreeStar, Ashland, OR).

### Quantitative real-time PCR (qRT-PCR)

On day 1 after GA induction, mouse synovium from different groups was freshly harvested. Total RNA was then extracted using a RNeasy lipid tissue mini kit (Qiagen). A NanoDrop 1000

(Thermo Fisher Scientific, Waltham, MA) was used to measure RNA quantity. Complimentary DNA (cDNA) was generated using the iScript cDNA synthesis kit (Vazyme, Nanjing, China) according to the manufacturer's manual. RT-PCR was performed on a QuantStudio 3 real-time PCR system or a QuantStudio 5 real-time PCR system (Applied Biosystems, Waltham, MA) using PowerUp SYBR Green Master Mix (Vazyme, Nanjing, China). The sequence of primers used was listed (Supplemental Table 2). Each sample was run in duplicate. The mRNA expression levels of target genes were analyzed using the $2^{-\Delta\Delta CT}$ method and was normalized to that of *Actb*.

**In vitro calcium imaging assay**

LAD2 cells ($1\times 10^5$) were loaded with 1 μM Fura-2-acetoxymethyl ester (Fura-2 AM; Invitrogen, Vilnius, Lithuania) in the loading buffer (same as the external solution used for patch clamp experiments) for 40-50 min at 37°C. Cells were subsequently washed three times and imaged in the external solution (same as those used for patch clamp experiments) at room temperature. An invert fluorescent microscope (Nikon ECLIPSE TE200; Melville, NY) was used for ratiometric $Ca^{2+}$ imaging. Fluorescent images under 340 and 380 nm excitation wavelengths were captured at 2 s intervals using a cooled CCD camera (ANDOR, Belfast, Northern Ireland) driven by a NIS-Elements software. The ratio of fluorescence intensity [$R_{(340/380)}$] obtained at 340 nm to 380 nm within a certain region of interest was used to reflect the changes in intracellular $Ca^{2+}$ signals. A cell was considered responsive to a stimulus if a change with R340/380 was equal or greater than 15% above baseline. SP (1 μM; Tocris, Bristol, UK) and complement 3a (C3a; 50 nM; Sigma, St Louis, MO) were applied to stimulate LAD2 cells.

**ELISA assay**

On day 1 after GA induction, synovial tissues were harvested from the knee of mice under urethane (1.5 g/kg; i.p.) anesthesia. The freshly diced tissues were homogenized with a high-speed KZ-III tissue homogenizer (Servicebio, Wuhan, China) and then centrifuged at 10,000 g for 10 min at 4°C. For mouse blood, serum was collected by centrifuging blood samples at 1,000 g for 10 min at 4°C. All the supernatants were harvested and tested for SP levels using a SP mouse ELISA kit (BBI Life Science, Shanghai, China) according to the manufacturer's instructions. The plate was read at 450 and 570 nm using a microplate reader (Molecular Devices, Sunnyvale, CA). The BCA assay kit (Beyotime, Shanghai, China) was used to quantify total protein of each sample.

**Supplementary figure legends**

**Supplementary Figure 1. No sexual dimorphism in analgesic effects of *Mrgprb2* deletion was observed in GA model mice. (A-H)** Comparison of mechanical threshold in the ankle (**A, E**), paw withdrawal frequency to 0.16 g in the hind paw (**B, F**), paw withdrawal latency (PWL) to radiant heat in the hind paw (**C, G**), joint diameter (**D, H**) between male (*Mrgprb2*$^{+/+}$, n = 10 mice; *Mrgprb2*$^{-/-}$; n = 9 mice) and female (*Mrgprb2*$^{+/+}$, n = 7 mice; *Mrgprb2*$^{-/-}$; n = 6 mice) mice of each genotype over the course of GA. *p< 0.05, **p < 0.01, ***p < 0.001 versus *Mrgprb2*$^{+/+}$; two-way ANOVA for repeated measures followed by Bonferroni post hoc test.

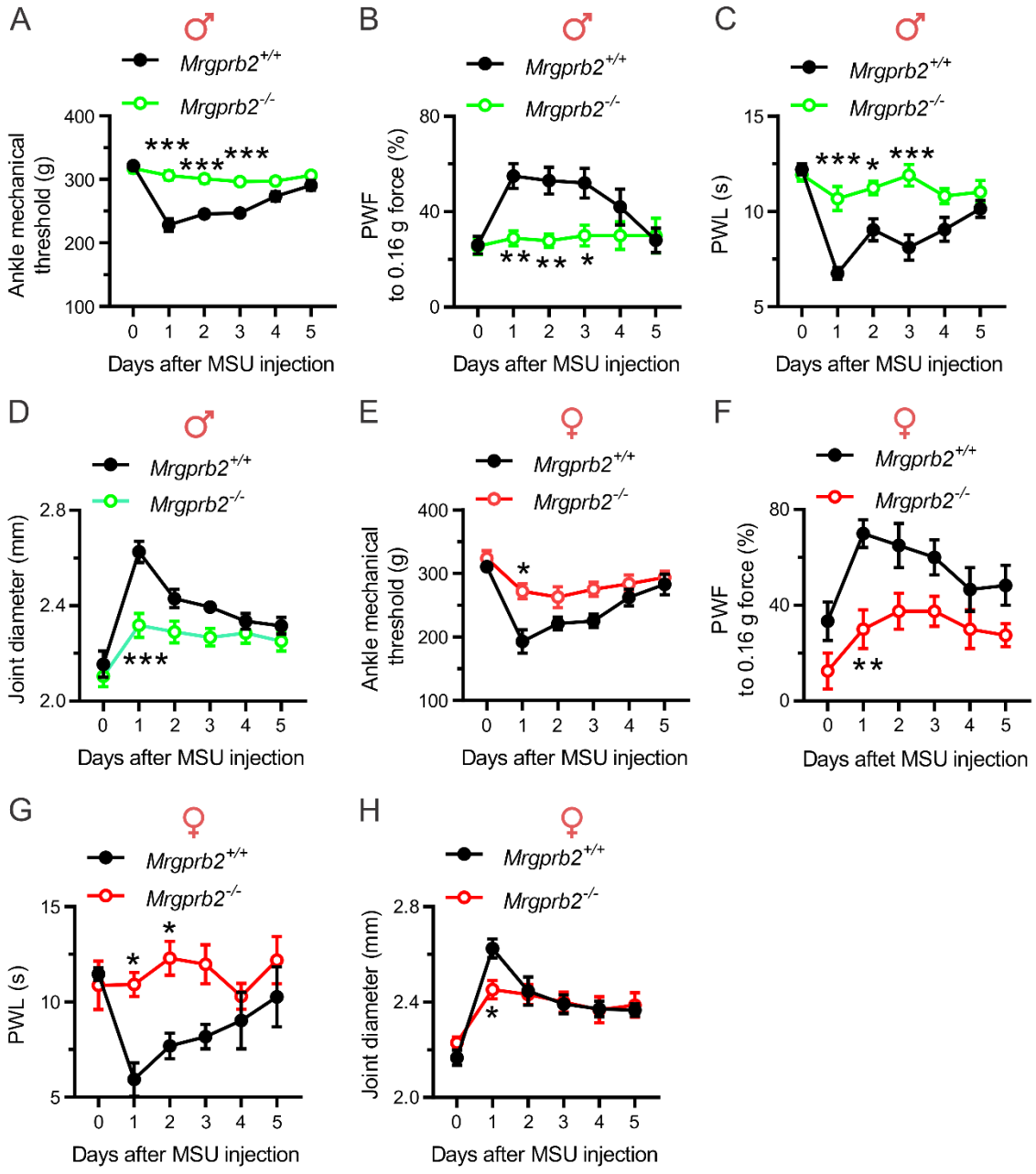
**Supplementary Figure 2.** Genetic deletion of *Mrgprb2* attenuates joint pain in CFA induced arthritis model. (**A-D**) Time course of ankle mechanical threshold (**A**), paw withdrawal frequency to 0.07 g (**B**), paw withdrawal latency to radiant heat (**C**), and ankle joint diameter (**D**) following intra-articular (i.a.) injection of CFA in *Mrgprb2*$^{+/+}$ (n = 8 mice) and *Mrgprb2*$^{-/-}$ mice (n = 7 mice); *p < 0.05, ** p < 0.01, ***P < 0.001 versus *Mrgprb2*$^{+/+}$, two-way repeated measures ANOVA followed by Bonferroni post hoc test.

**Supplementary Figure 3. *Mrgprb2*$^{-/-}$ mice exhibit no deficits in the number of synovial MCs.** (**A**) Representative sections of knee joints from *Mrgprb2*$^{+/+}$ and *Mrgprb2*$^{-/-}$ mice and stained with c-Kit and DAPI. S: synovium. Scale bar: 100 μm. (**B**) No significant difference in the number of synovial MCs was observed between genotypes. n = 5 mice per group; P > 0.05; unpaired Student's t test.

**Supplementary Figure 4. MSU fails to induce degranulation in LAD2 cells.** (**A**) β hexosaminidase (β-hex) release in LAD2 cells induced by MSU (250, 500, 1000 μg/ml), C48/80

(20 μg/ml) and vehicle (Veh; PBS). n = 8 experiments per group. ***$p < 0.001$ versus Veh; one-way ANOVA followed by Tukey's test.

**Supplementary Figure**

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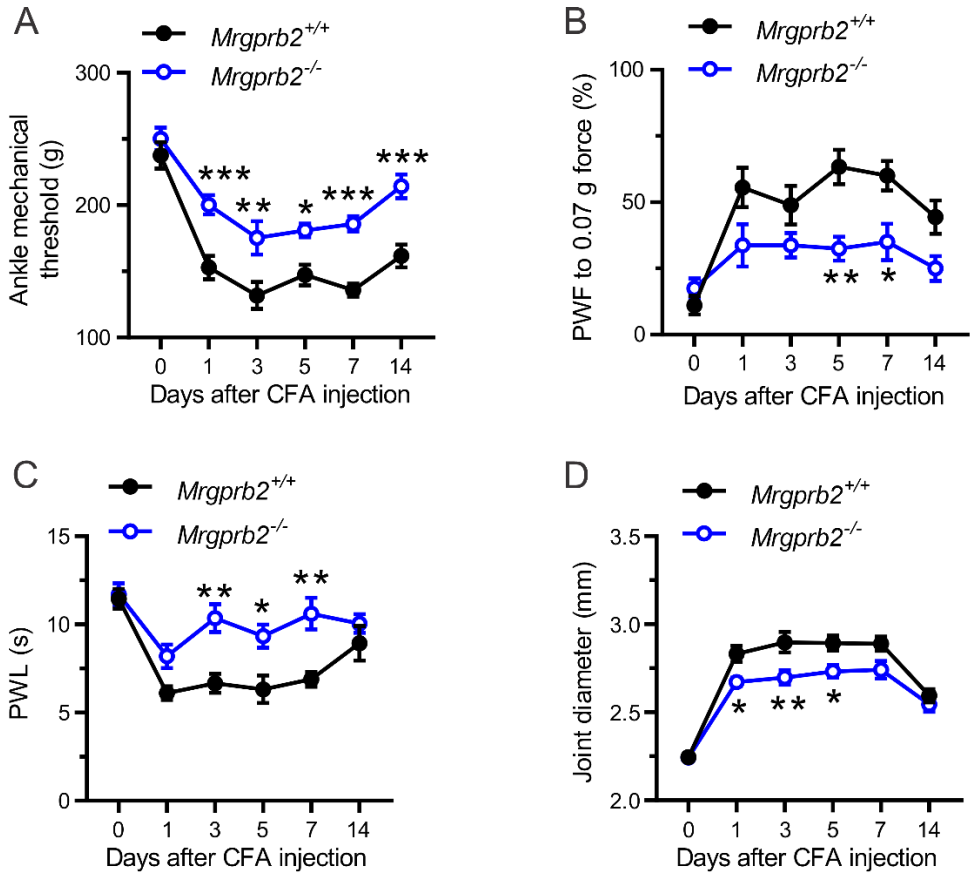


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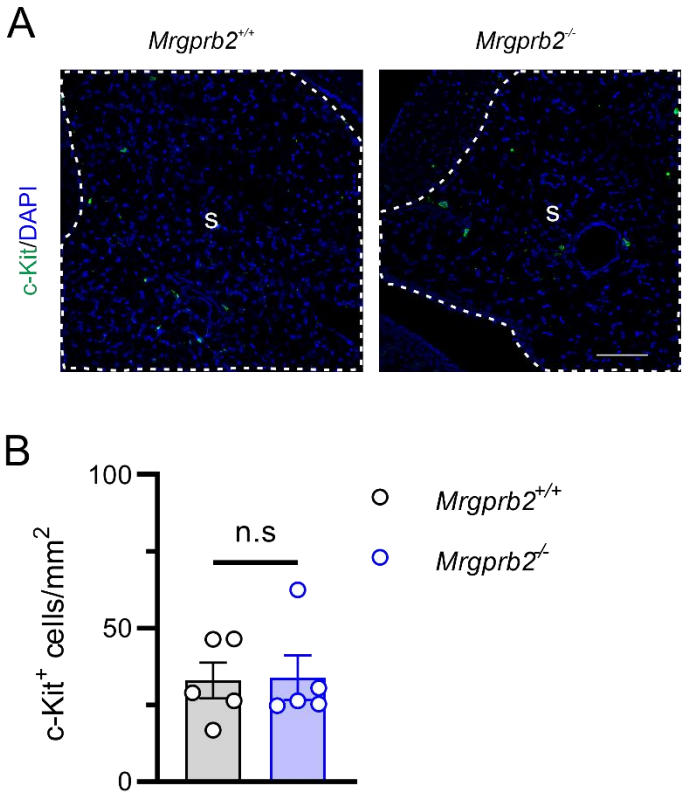


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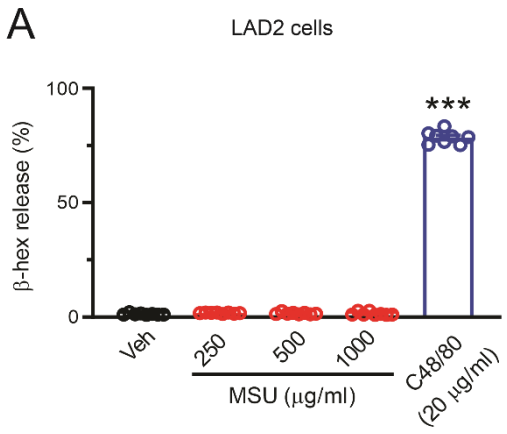


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**Table S1. Key resources table**

| Regent or Resource | Dilution | Source | Identifier |
|---|---|---|---|
| Antibodies | | | |
| Goat anti-c-Kit | 1:1000 | R&D system | Cat# AF1356 |
| Rat anti-CD45 | 1:500 | Sigma | Cat# 05-1416 |
| Rat anti-CD68 | 1:500 | Biolegend | Cat# 137001 |
| Rat anti-Ly6G | 1:1000 | Biolegend | Cat# 127601 |
| Rabbit anti-PGP9.5 | 1:1000 | Abcam | Cat# ab108986 |
| Rabbit anti-HA | 1:200 | Cell Signaling Technology | Cat# 3724 |
| Rabbit anti-c-Fos | 1:1000 | Sigma | Cat# ABE457 |
| Chicken anti-NeuN | 1:200 | Aves | Cat# NUN-0020 |
| Goat anti-mCherry | 1:250 | ORIGENE | Cat# AB0040 |
| Donkey anti-Rat IgG Alexa 488 | 1:250 | Jackson ImmunoResearch labs | Cat# 712-545-153 |
| Donkey anti-Rabbit IgG Alexa 488 | 1:250 | Jackson ImmunoResearch labs | Cat# 711-545-152 |
| Donkey anti-Rabbit IgG Alexa 647 | 1:250 | Jackson ImmunoResearch labs | Cat# 711-605-152 |
| Donkey anti-Goat IgG Alexa 488 | 1:250 | Jackson ImmunoResearch labs | Cat# 705-545-147 |
| Donkey anti-Chicken Alexa 488 | 1:250 | Jackson ImmunoResearch labs | Cat# 703-545-155 |
| Donkey anti-Goat IgG Alexa 594 | 1:250 | Abcam | Cat# ab150132 |
| PE anti -mouse CD45 | 1:100 | Biolegend | Cat# 103105 |
| FITC anti-mouse CD11b | 1:100 | Biolegend | Cat# 101205 |
| APC anti-mouse Ly6G | 1:100 | Biolegend | Cat# 127613 |
| APC anti-mouse c-Kit | 1:100 | Biolegend | Cat# 135108 |
| FITC anti-mouse FcεRI | 1:100 | Biolegend | Cat# 134305 |
| PE anti-human CD117 | 1:100 | Milltenyi Biotec | Cat# 130114070 |
| APC anti-human MRGPRX2 | 1:100 | Biolegend | Cat# 359005 |
| FITC anti-human CD45 | 1:100 | Biolegend | Cat# 304006 |
| Anti-mouse CD32/16 Fc Blocker | 1:100 | eBioscience | Cat# 14016182 |
| Chemicals, peptides, reagents | | | |

| | | |
|---|---|---|
| Avidin-FITC | Sigma | Cat# A2050 |
| MSU | Sigma | Cat# U2875 |
| CFA | Sigma | Cat# F5881 |
| 7-AAD | BD Pharmingen | Cat# 516898 |
| Substance P | Tocris | Cat# 1156 |
| Compound 48/80 | Sigma | Cat# C2313 |
| Complement 3a | Sigma | Cat# 204881 |
| CNO | Tocris | Cat# 4936 |
| Osthole | MCE | Cat# HY-N0054 |
| Dil | Sigma | Cat# 42364 |
| Fura-2 AM | Invitrogen | Cat# F1221 |
| PNAG | Sigma | Cat# 487052 |
| Anti-SP antibody for pain studies | Millipore Sigma | Cat# AB1566 |
| Isotype IgG for pain studies | Senbeijia | Cat# SBJ-SE-RAB0001 |
| Liberase TM | Roche Diagnostics Corp | Cat# 0540119001 |
| Liberase TL | Roche Diagnostics Corp | Cat# 05401020001 |
| Papain | Worthington Biochemical | Cat# LS003126 |
| Bovine serum albumin | Sigma | Cat# A9418 |
| Hyaluronidase | Sigma | Cat# H3506 |
| Collagenase type IA | Sigma | Cat# C9891 |
| Collagenase VIII | Sigma | Cat# C2139 |
| Dnase I | Sigma | Cat# 11284932001 |
| Human SCF | Peprotech | Cat# 300–07 |
| Murine SCF | Peprotech | Cat# 250-03 |
| Murine IL-3 | Peprotech | Cat# 213-13 |
| SP ELISA Kit | BBI Life Science | Cat# D751030 |

**Table S2 List of DNA primer sequences for qRT-PCR**

| Target gene | Forward 5'-3' | Reverse 5'-3' |
|---|---|---|
| *Tac1* | TTTCTCGTTTCCACTCAACTGTT | GTCTTCGGGCGATTCTCTGC |
| *Tnfa* | AGCAGAAGCTCCCTCAGCGAGG | TCCACGTCGCGGATCATGCTTT |
| *Il1b* | GGAGAACCAAGCAACGACAAAATA | TGGGGAACTCTGCAGACTCAAAC |
| *Cxcl1* | ATCCAGAGCTTGAAGGTGTTG | GTCTGTCTTCTTTCTCCGTTACTT |
| *Sphk1* | CGTGGACCTCGAGAGTGAGAA | AGGCTTGCTAGGCGAAAGAAG |
| *Actb* | CTGAATGGCCCAGGTCTGA | CCCTGGCTGCCTCAACAC |

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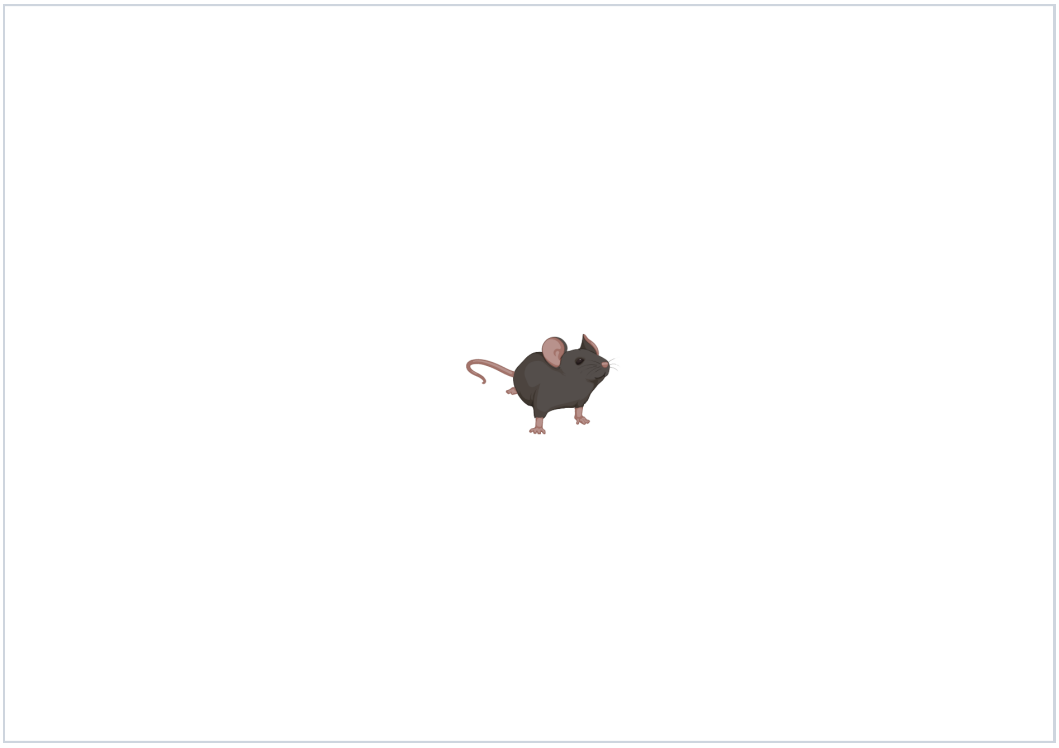

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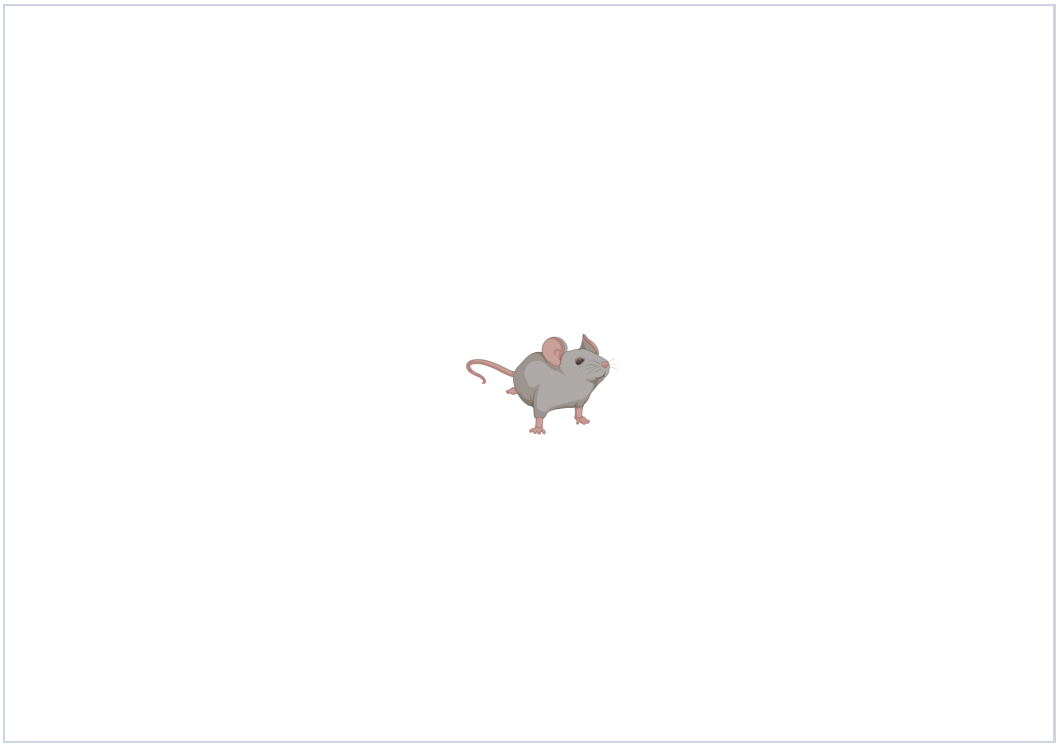

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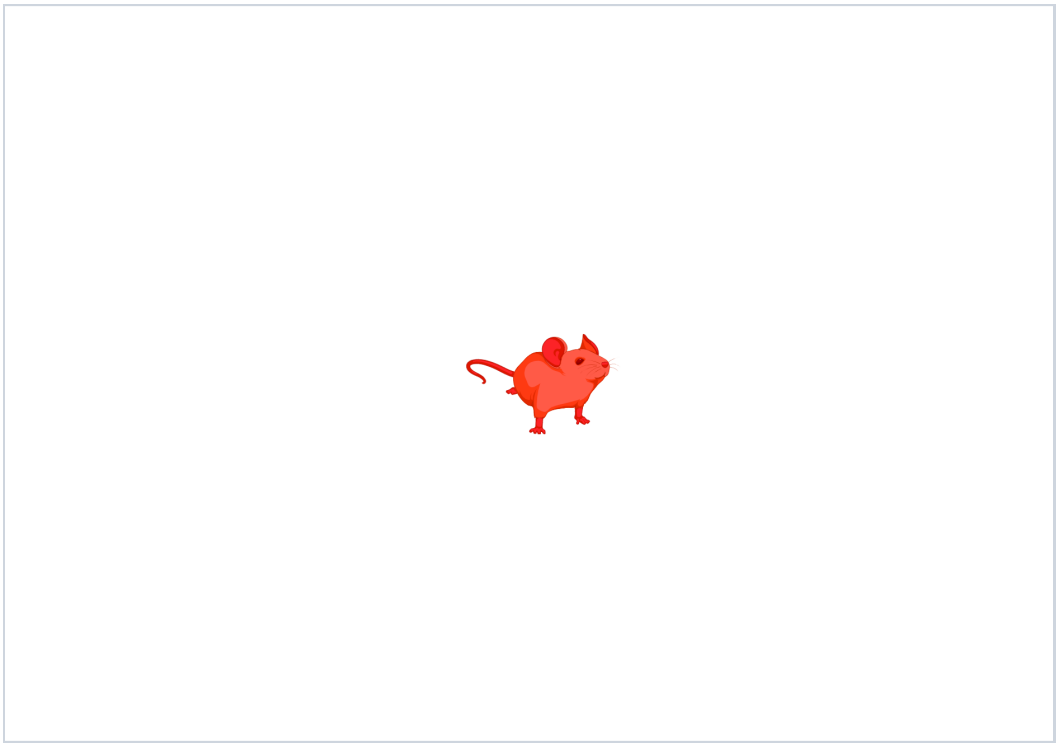

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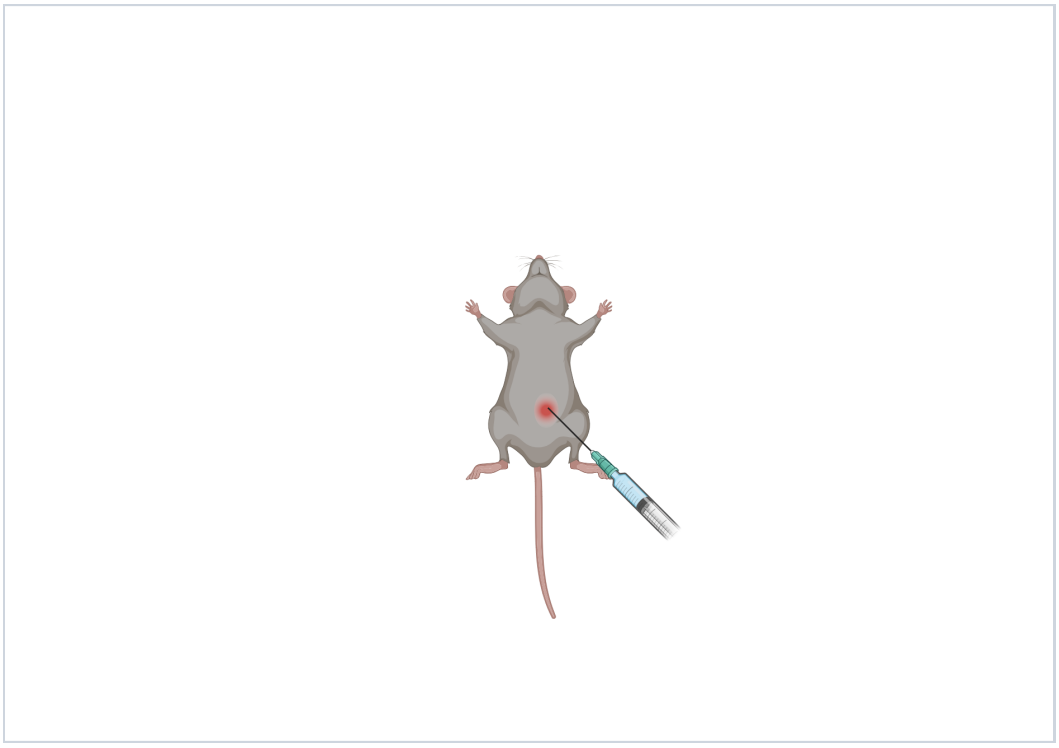

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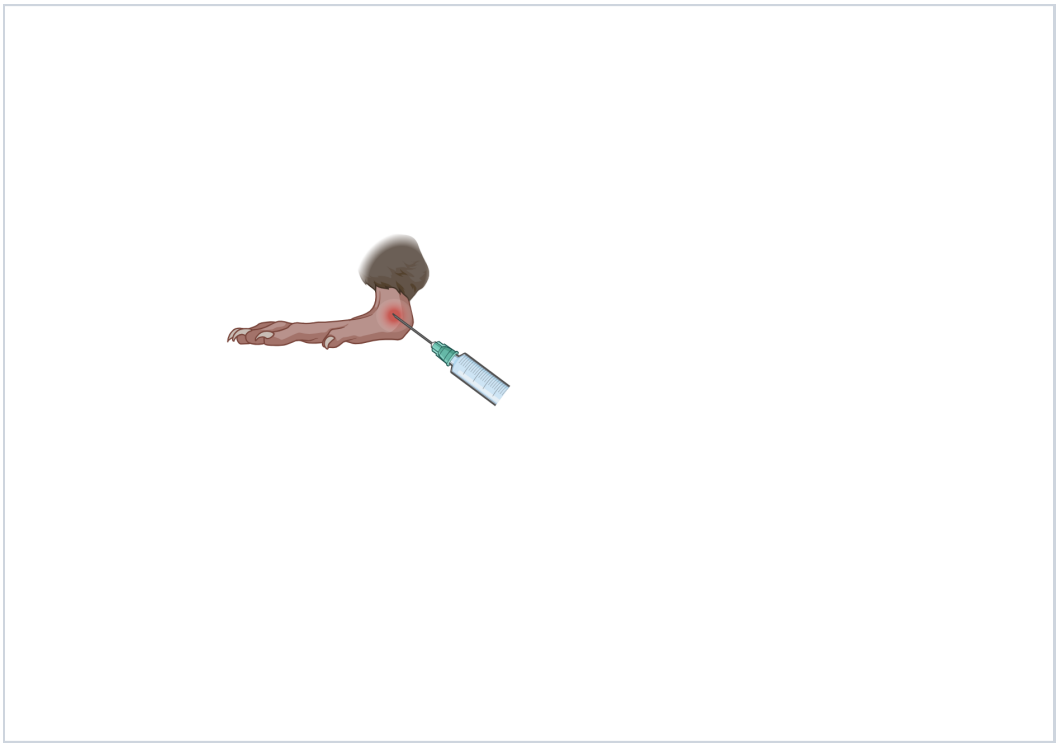

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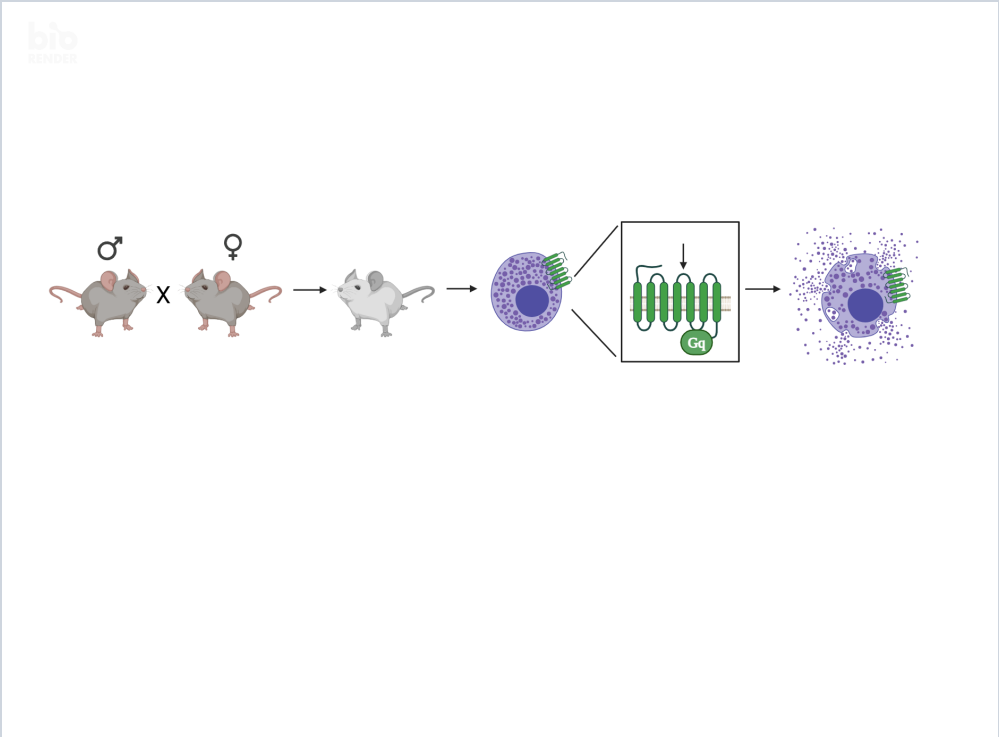


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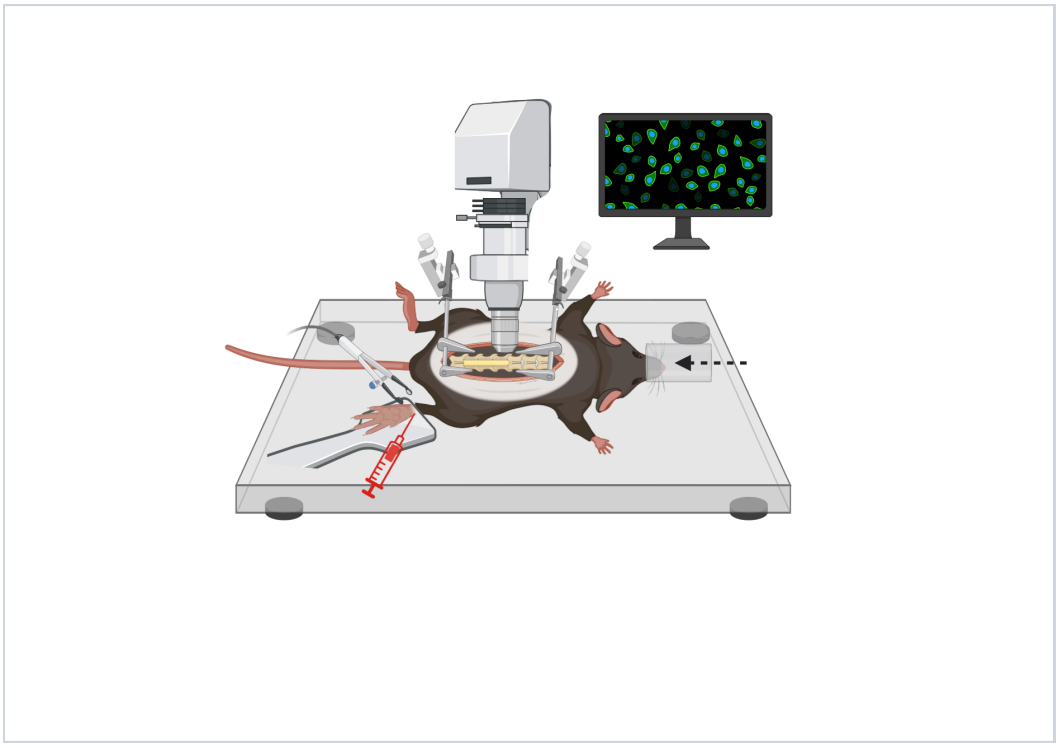

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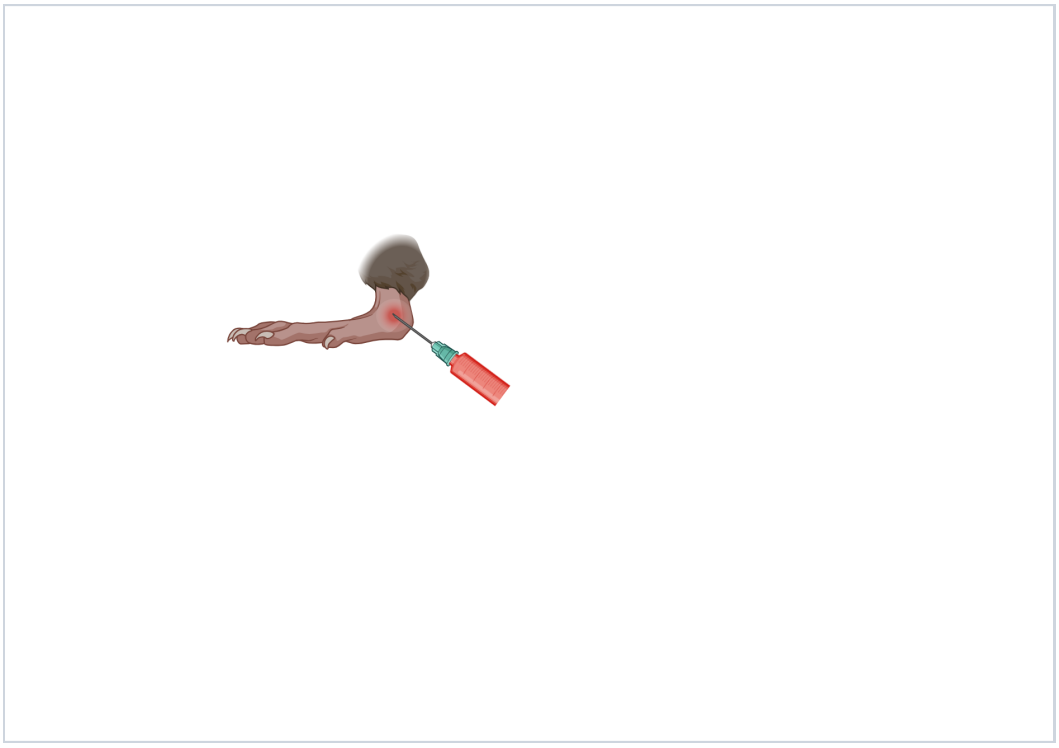

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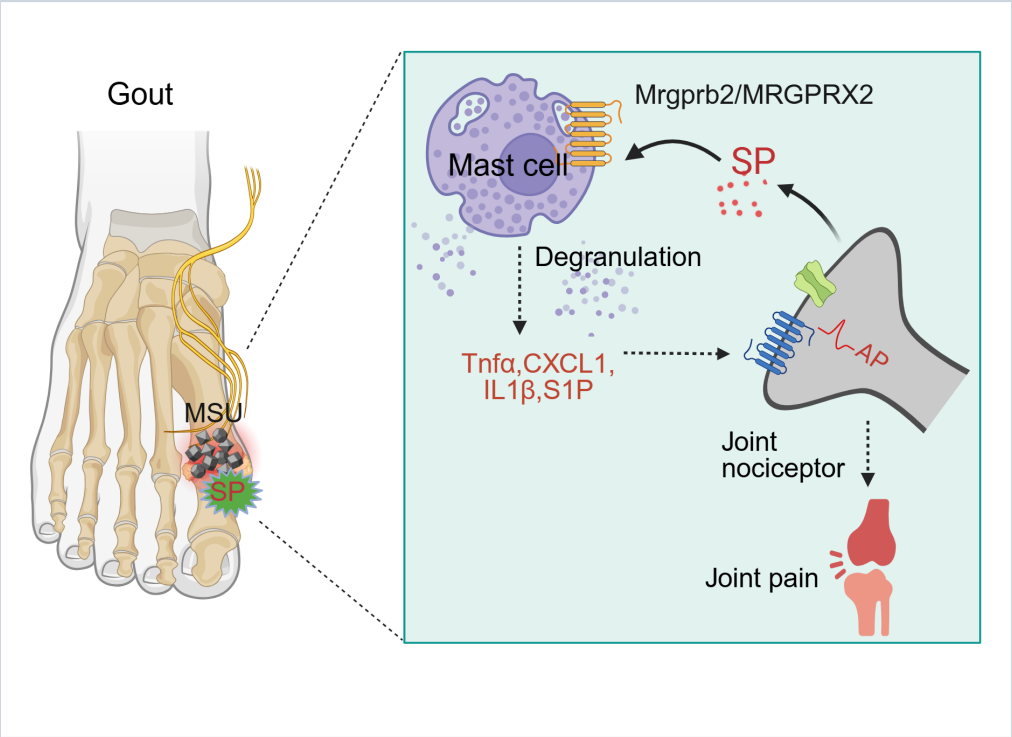


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