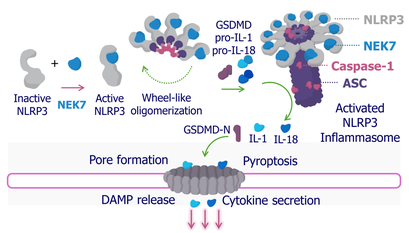
# #1082
# MRT-8102, an Orally Bioavailable NEK7-Selective Molecular Glue Degrader, Suppresses NLRP3 Inflammasome Activation and Demonstrates Efficacy in a Rabbit Model of Gouty Arthritis

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## NEK7 Licenses NLRP3 Inflammasome Assembly



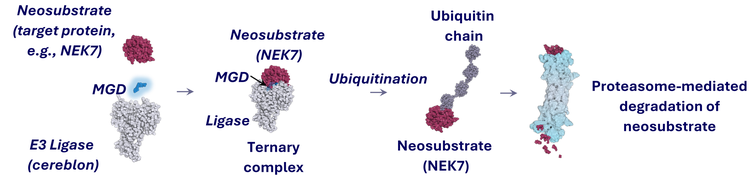

**NLRP3-Driven Inflammatory Diseases**
(selected examples)



| Joints | Skin | Cardiovascular disease | |
|---|---|---|---|
| Gout | Hidradenitis suppurativa | Pericarditis STEMI | Atherosclerosis |

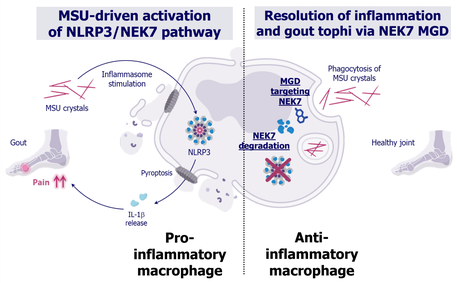
- The NLRP3 inflammasome is a multi-protein complex that triggers the generation of pro-inflammatory cytokines such as interleukin (IL)-1 and IL-18 in response to cell stress.
- Activation of the NLRP3 inflammasome depends on **NIMA-related kinase 7, or NEK7**, a critical serine/threonine-protein kinase that facilitates assembly of the active NLRP3 inflammasome complex in a kinase-independent manner.
- NEK7 degradation constitutes a novel approach to modulating the NLRP3 inflammasome, which may have broad therapeutic implications in a variety of inflammatory diseases, including crystal arthropathies such as gout.

## MRT-8102 is an Oral, Highly Selective, NEK7 MGD




Molecular glue degraders (MGDs) create novel recognition interfaces on the surface of E3 ubiquitin ligases such as cereblon (CRBN) to recruit target proteins for degradation by the ubiquitin-proteasome system. MGDs are attractive not only for their ability to induce protein-protein interactions and eliminate their molecular targets, but also for their favorable physicochemical properties and associated developability compared to Proteolysis Targeting Chimeras (PROTACs).
At the time of abstract submission, MRT-8102 was being evaluated in a Phase 1 study including healthy subjects and participants at cardiovascular risk with elevated CRP (NCT07119125). At time of poster presentation, MRT-8102 has shown normalization of key pathogenic drivers of atherosclerotic cardiovascular disease (ASCVD) in subjects with elevated CVD risk.

## MRT-8102 for Gout Treatment: Rationale

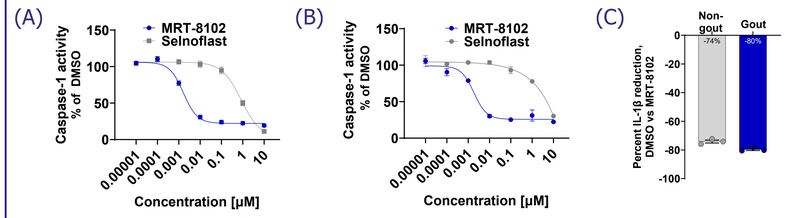



- Gout is a canonical NEK7/NLRP3 pathway disease: monosodium urate (MSU) crystals trigger NEK7-mediated NLRP3 complex assembly, driving release of IL-1β and DAMPs, and inducing flare pathology.
- Blocking NLRP3 signaling via NEK7 degradation may therefore relieve inflammation and pain in patients with recurrent gout flares.
- 70% of patients experience flares within three months of pegloticase treatment likely due to dissolution of tophi and resulting MSU-induced NLRP3 activation.

## Objectives

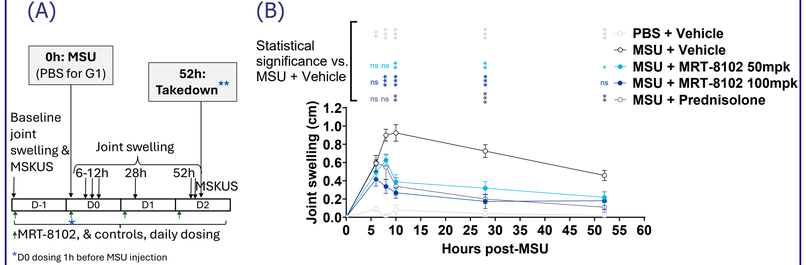
To evaluate the anti-inflammatory and disease-modifying activity of NEK7 degradation by MRT-8102 in human NLRP3 inflammasome activation systems and in a preclinical model of gout.

## Fig 1. MRT-8102 Inhibited NLRP3 Activation in (A) MSU-, (B) CPPD-Stimulated hMDM, and (C) Whole Blood From Donors Diagnosed with Gout



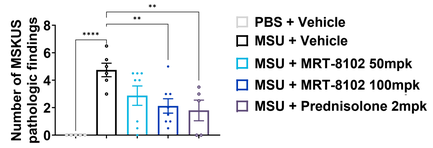

(A, B) Human monocyte-derived macrophages (hMDM) were incubated with MRT-8102 or the NLRP3 inhibitor, selnoflast, for 20 h. Cells were then stimulated with LPS and MSU (A) or calcium pyrophosphate dihydrate (CPPD) crystals for 6 h. Caspase-1 activity was measured in the supernatants using a luminescent inflammasome assay.
(C) Whole blood from donors with gout (diagnosed within 5 years) and non-gout donors was stimulated with LPS + Nigericin, in the presence of MRT-8102 or DMSO as control. IL-1β levels in the supernatant were measured by ELISA. Data normalized to DMSO-treated control samples represent mean ± SEM.

## Fig 2. MRT-8102 Treatment Reduced Joint Swelling in Rabbit Gout



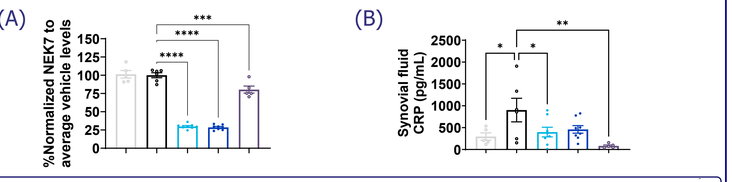

(A) Study design: New Zealand white rabbits were randomized based on body weights into the following treatment groups: PBS + vehicle (n=5); MSU + vehicle (n=6); MSU + MRT-8102 50 or 100 mpk p.o. (n=8 each); MSU + prednisolone 2 mpk s.c. (n=5). At baseline (Day -1), body weight, joint swelling and musculoskeletal ultrasound (MSKUS) of the knee joints were recorded as a reference for MSU-induced changes. All groups were given prophylactic dosing of MRT-8102, prednisolone, or vehicle (0.5% methyl cellulose) dosed daily from Day -1. On Day 0, rabbits received a single intra-articular injection of 1 mL of MSU crystals (50 mg/mL) into each knee (MSU groups), or 1 mL of phosphate-buffered saline (PBS), as vehicle.
(B) The degree of joint swelling was determined by measuring knee perimeter with a digital caliper, data presented as mean ± SEM, and differences assessed via a two-way ANOVA test with Dunnett's multiple comparisons; *p<0.05, **p<0.01, ***p<0.001.

## Fig 3. MRT-8102 Treatment Reduced Musculoskeletal Ultrasound Composite Scores



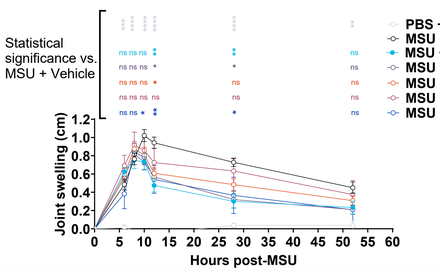

Musculoskeletal ultrasound (MSKUS) composite score at takedown. Seven findings were each scored present (1) or absent (0) per joint: global joint distension, synovial fluid, increased synovial thickening, intra-synovial power Doppler signal, isoechoic sand-like material, hyperechoic aggregates, and bright foci within sand-like material. The composite is their sum (range 0–7). Data presented as mean ± SEM, symbols representing individual animals. One-way ANOVA with Dunnett's multiple comparisons vs MSU + vehicle; **p<0.01, ***p<0.001.

## Fig 4. MRT-8102 Treatment Induced NEK7 Degradation in vivo & Led to Reduced Synovial Fluid C-reactive protein (CRP)




All rabbits were euthanized 4 hours after the 4th dose, and blood, joints, spleen, and synovial fluids were collected.
(A) Concentrations of NEK7 in rabbit spleens were analyzed using a Jess Simple Western method.
(B) Synovial fluid from left knees were tested for the presence of CRP by ELISA. Symbols represent individual animals. Data presented as mean ± SEM and assessed with a one-way ANOVA test with Dunnett's multiple comparisons; *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

## Fig 5. MRT-8102 Performed Comparably to Select Clinical and Mechanistic (NLRP3 inhibitor) Benchmarks




A second study was performed per Fig. 2A's design. Groups included PBS + vehicle (n=4); MSU + vehicle (n=7); MRT-8102 50 mpk p.o. (n=6); colchicine 0.2 mpk s.c. (n=6); prednisolone 2 mpk s.c. (n=5); MCC950 20 mpk p.o. (n=6); Berzanoflast 10 mpk p.o. (n=6). Data presented as mean ± SEM and assessed with two-way ANOVA test with Dunnett's multiple comparisons; *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

## GEMINI-1*: A Phase 2 Study in Gout Flare Prevention Following Acute Flare Management

**GEMINI: Glue Elimination of Monosodium urate-Induced NEK7 Inflammation*

**Proposed trial design subject to review by FDA:**

**Goals**
- Dose exploration
- Safety and efficacy
- Establish PoC for flare prevention following acute flares

**Population**
- ~ 60 patients
- Recurrent gout flares

Randomization:
- MRT-8102 dose level 1
- MRT-8102 dose level 2

Enrollment → 12 weeks treatment

**Outcome measures and PoC expectation**
- Reduction in pain visual analog scale by 72 hours
- Frequency of new flares

Study initiation planned for Q4 2026 / Q1 2027; data update expected in H2 2027

## Summary and Future Development

- NEK7 is a critical component of the NLRP3 inflammasome; MRT-8102 is an oral NEK7 molecular glue degrader.
- In vitro, MRT-8102 reduced caspase-1 activity in macrophages stimulated with MSU or CPPD crystals and suppressed IL-1β release in whole blood from both gout and non-gout donors.
- In vivo, MRT-8102 treatment reduced joint swelling comparably to prednisolone and clinical or mechanistic benchmarks; MRT-8102 treatment also improved the MSKUS composite score.
- MRT-8102 treatment induced spleen NEK7 degradation and reduced synovial CRP, consistent with pathway engagement upstream of the NLRP3 / IL-1 / IL-6 / CRP axis.
- These data support NEK7 degradation as a novel strategy to inhibit NLRP3 inflammasome activation in (pseudo)gout, with relevance to other NLRP3-driven inflammatory diseases.

***Abbreviations:*** ***ANOVA:*** *analysis of variance;* ***ASC:*** *apoptosis-associated speck-like protein containing a caspase recruitment domain;* ***ASCVD:*** *atherosclerotic cardiovascular disease;* ***CPPD:*** *calcium pyrophosphate dihydrate;* ***CRBN:*** *cereblon;* ***CRP:*** *C-reactive protein;* ***DAMP:*** *damage-associated molecular pattern;* ***DMSO:*** *dimethyl sulfoxide;* ***ELISA:*** *enzyme-linked immunosorbent assay;* ***GSDMD(-N):*** *gasdermin D (N-terminal fragment);* ***hMDM:*** *human monocyte-derived macrophages;* ***IL:*** *interleukin;* ***LPS:*** *lipopolysaccharide;* ***MGD:*** *molecular glue degrader;* ***mpk:*** *milligram per kilogram;* ***MSU:*** *monosodium urate;* ***NEK7:*** *NIMA-related kinase-7;* ***NLRP3:*** *NOD-like receptor pyrin domain-containing protein 3;* ***PBS:*** *phosphate-buffered saline;* ***p.o.:*** *per os (orally);* ***PoC:*** *proof of concept;* ***PROTACs:*** *proteolysis targeting chimeras;* ***s.c.:*** *subcutaneously;* ***SEM:*** *standard error of the mean;* ***STEMI:*** *ST-elevated myocardial infarction.*

**Disclosures:** All authors are employees of Monte Rosa Therapeutics and may hold stock or stock options in the company. This study was funded by Monte Rosa Therapeutics.