Targeting NLRP3 Inflammasome Activation and Inflammation in Gout with NEK7 Molecular Glue Degraders: A Novel Therapeutic Strategy

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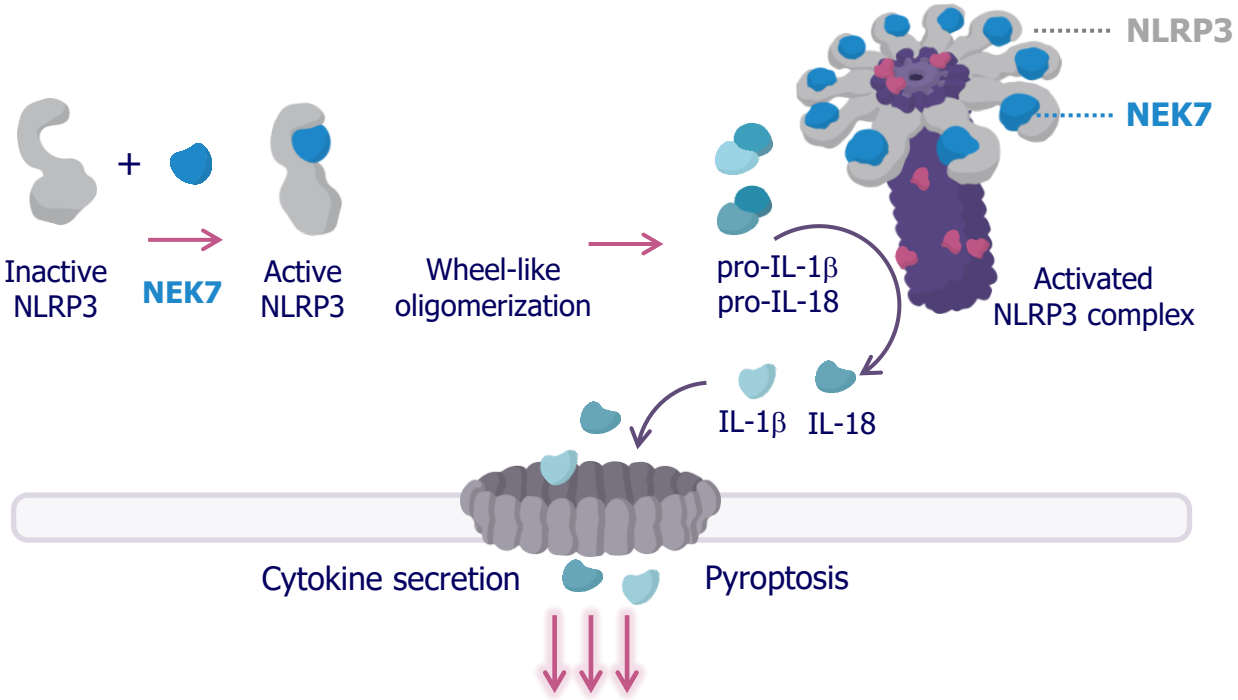
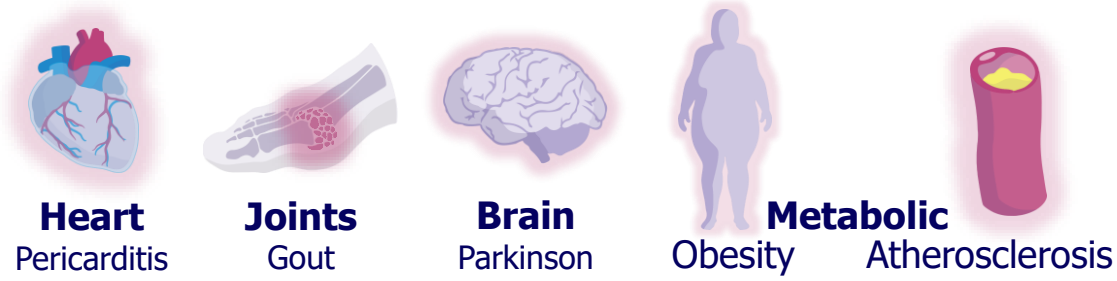
Monte Rosa Therapeutics

Targeting NLRP3 Inflammasome Activation and Inflammation in Gout with NEK7 Molecular Glue Degraders

- NEK7 as a Critical Component of NLRP3 Inflammasome-driven Gout
- Utilizing a Molecular Glue Degrader, MRT-8102, to Target NEK7/NLRP3 inflammasome
- PKPD of MRT-8102, a NEK7 MGD
- Gout as a Clinical Opportunity

NEK7 is a Key Regulator of NLRP3 Inflammasomes, IL-1 and IL-18





Therapeutic Hypothesis:

Activation of the NLRP3 inflammasome critically depends on NEK7

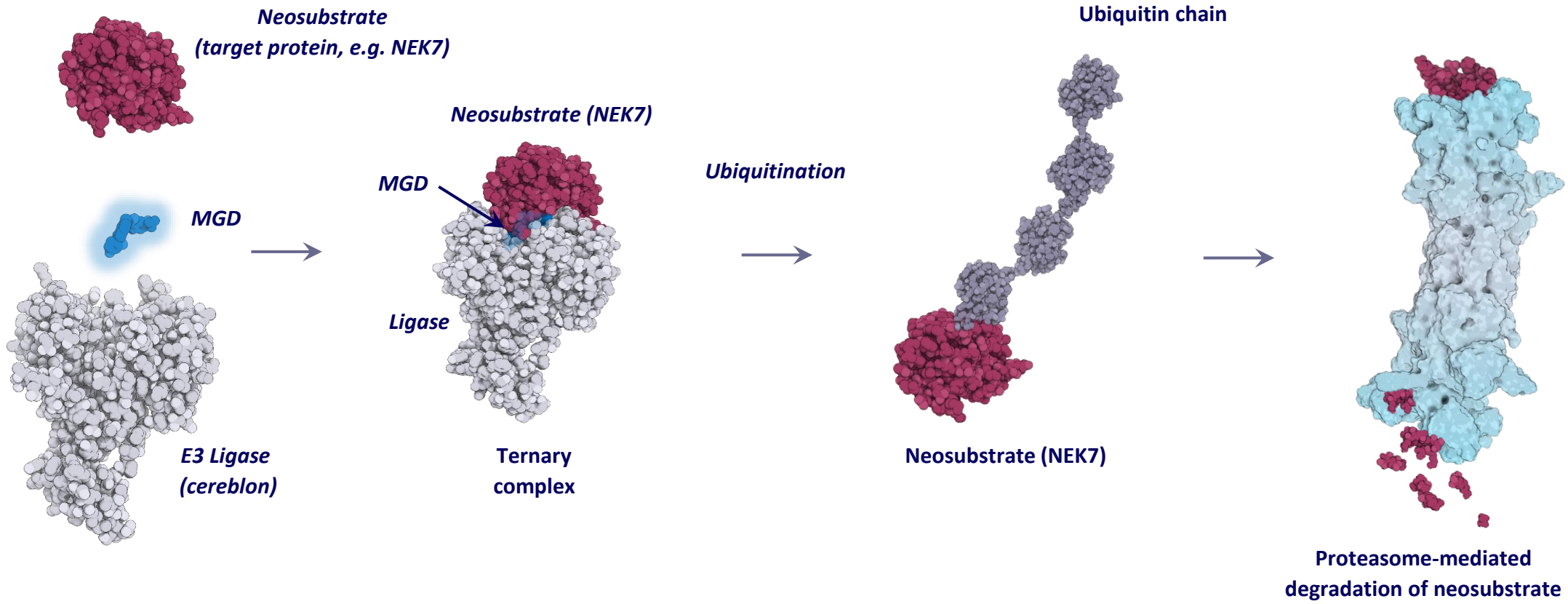
- NEK7 licenses NLRP3 assembly in a kinase-independent manner
- NEK7-deficient macrophages are severely impaired in IL-1β and IL-18 secretion

Consequently, NEK7 degradation has the potential to become an important treatment modality for a variety of inflammatory diseases

Clinical Opportunity:

Diseases driven by IL-1 and the NLRP3 inflammasome including gout, pericarditis and other cardiovascular disease, neurodegenerative disease, and obesity

Our Novel Approach To Targeting the NLRP3 Inflammasome Through NEK7 Degradation With Molecular Glue Degraders (MGDs)



Monte Rosa's rationally designed MGDs have potential applications in Oncology, Immunology, Neuroscience and other therapeutic areas

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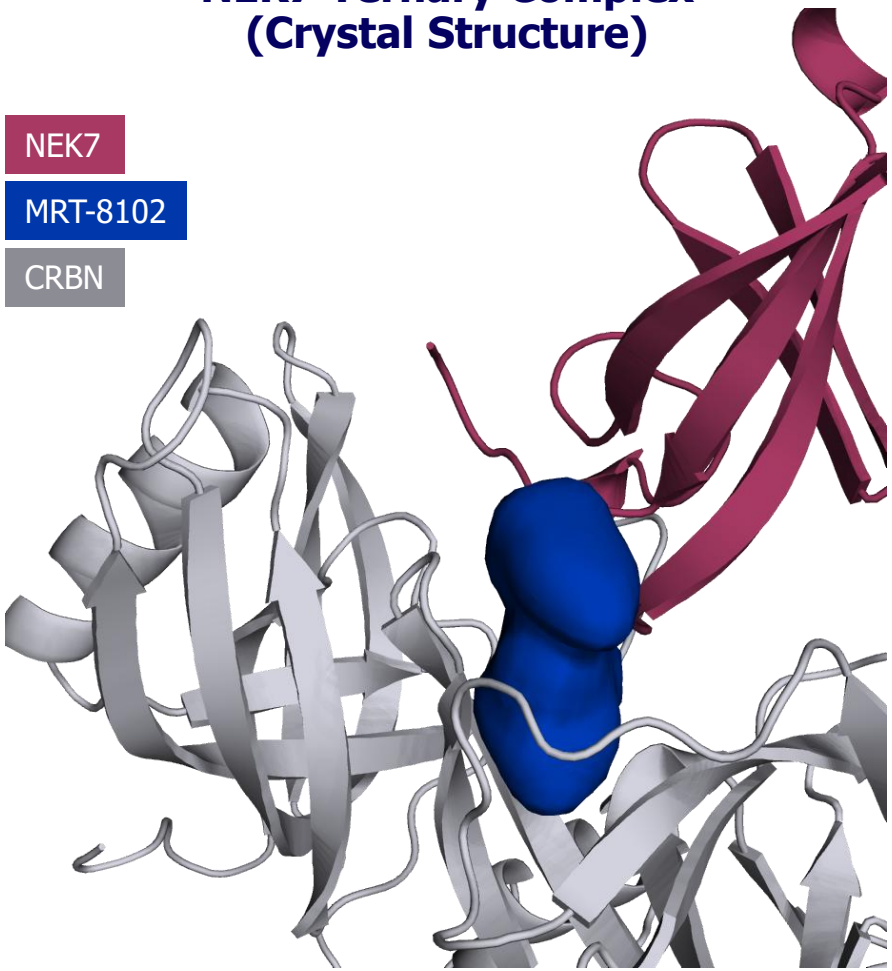
MRT-8102 is a Potent, Selective NEK7-Directed MGD With a Favorable Drug-like Profile

NEK7 Ternary Complex (Crystal Structure)

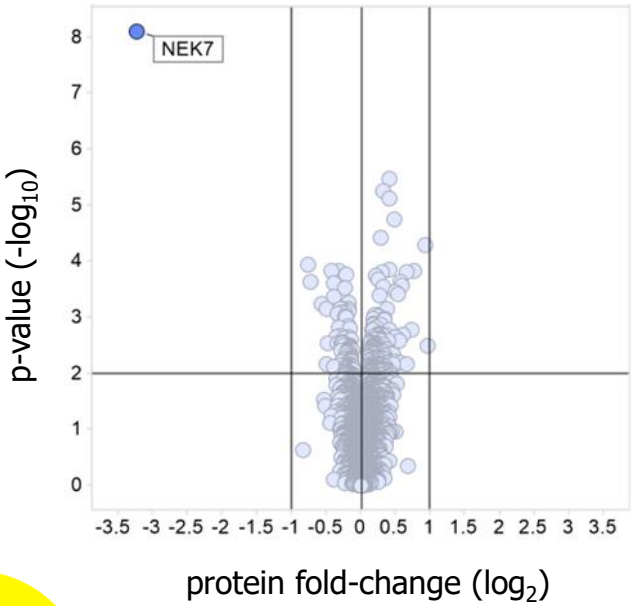


MGD Activity Profile	
CRBN Binding (HTRF, IC_{50})	0.2 µM
NEK7 Degradation (CAL51, DC_{50} /Dmax)	10 nM / 89%
Selectivity (TMT proteomics)	Excellent selectivity profile in different cell lines
Species activity	Active in human and non-human primates Not active in rodents
Physicochemical Properties	
LogD	1.47
MW	<450
Thermodynamic Solubility	166 µM
ADMET Profile	
Oral Bioavailability	Yes
Metabolite Profile (*in vitro*)	No unique human metabolites or GSH adducts (mics)
Safety Pharmacology	
Mini-Ames	Negative
hERG (patch clamp)	No inhibition (EC50> 30 µM)
Counterscreens (panel with 44 proteins)	No inhibition

MRT-8102 Is Selective and Potent Inhibitor of NLRP3 Inflammasome Activity

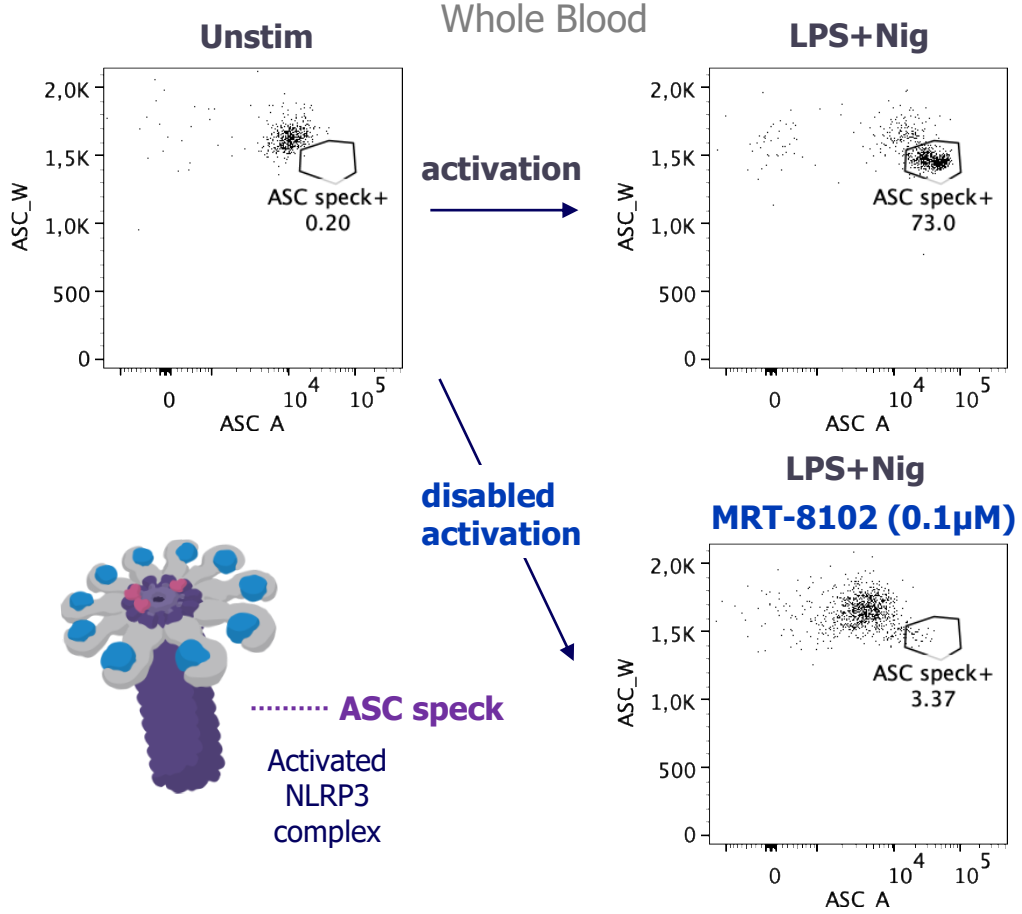
Selectivity

hPBMC

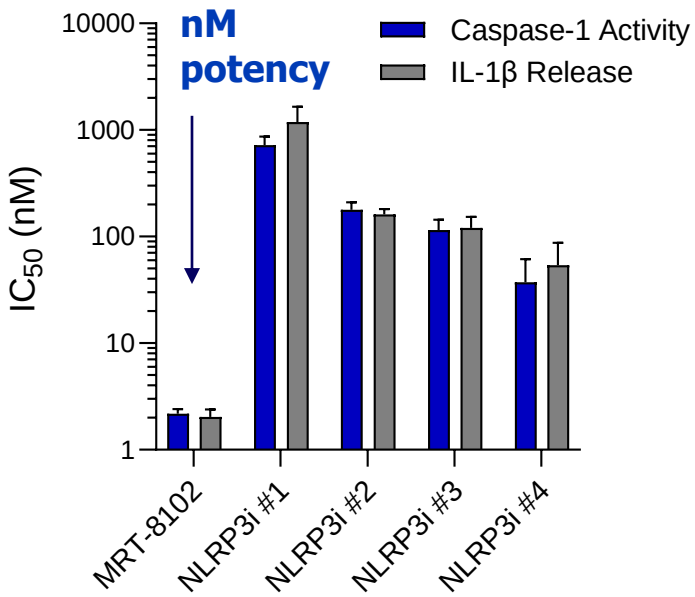


Functional Inhibition

Human Whole Blood



hMDM LPS + Nig



Nig = nigericin
hMDM = human monocyte-derived macrophages
hPBMC = human peripheral blood mononuclear cells

Gating strategy: Single cells, CD45+, CD66b-, CD14+

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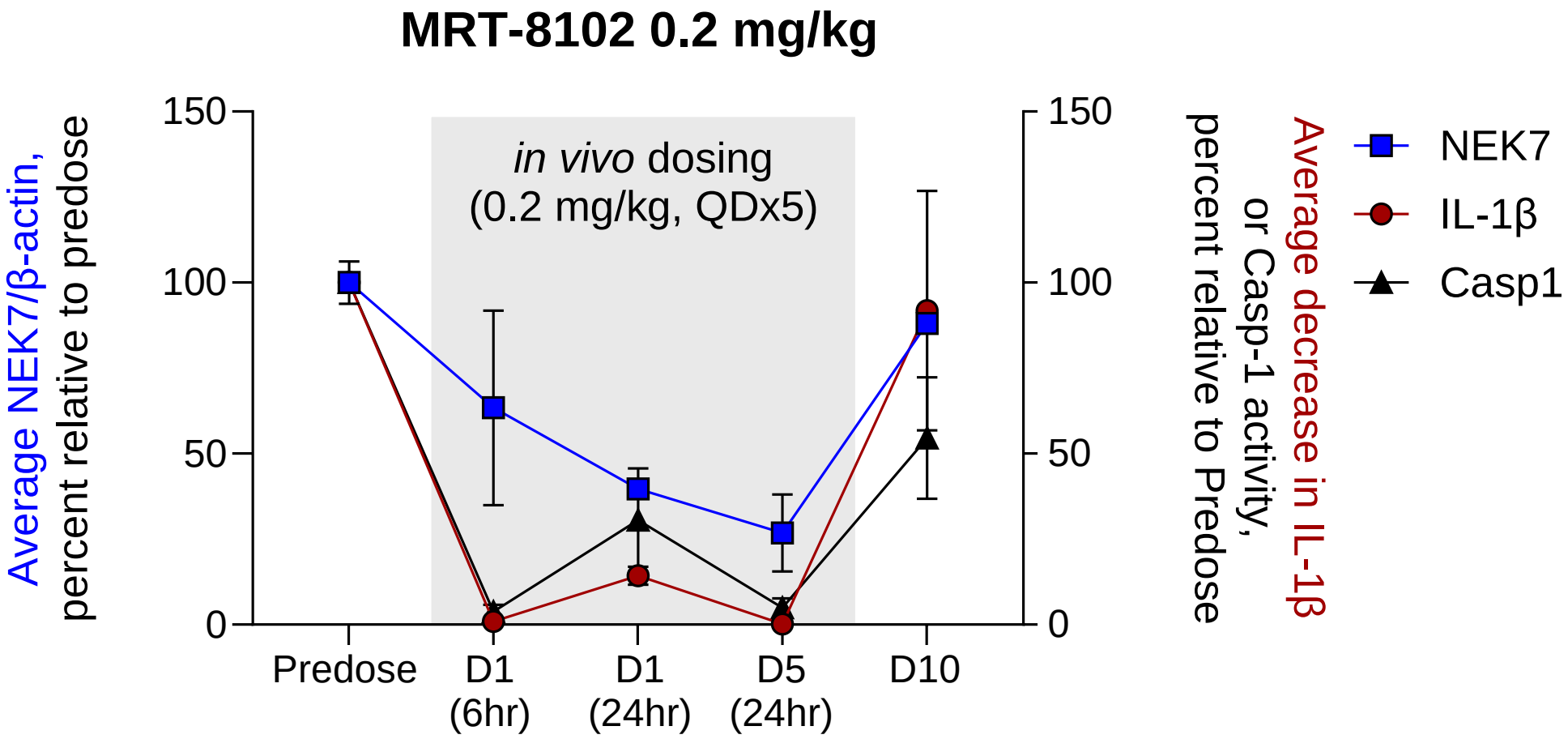
In Vivo Proof-of-mechanism for NEK7 MGD MRT-8102 in Cynomolgus Monkey

In vivo NEK7 degradation leads to inhibition of NLRP3 inflammasome in *ex vivo* stimulation assay



- IL-1β in plasma after *ex vivo* stimulation with LPS + nigericin; $n = 2$
- Follow-up study with 1 mg/kg MRT-8102, *i.v.* at 4 hr showed similar results

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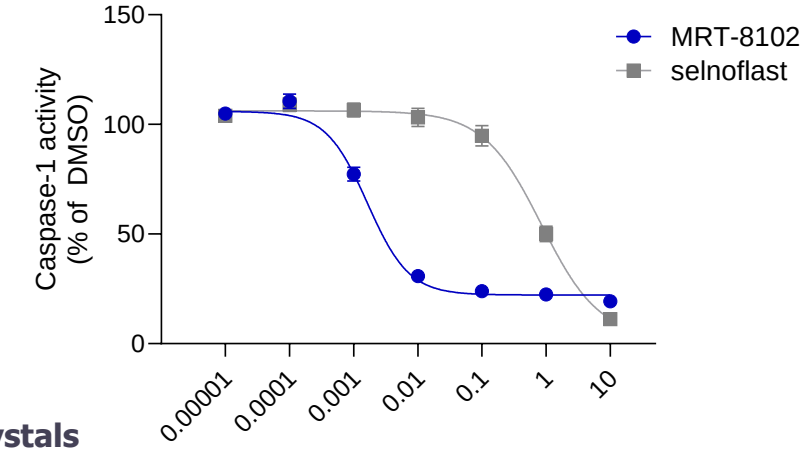
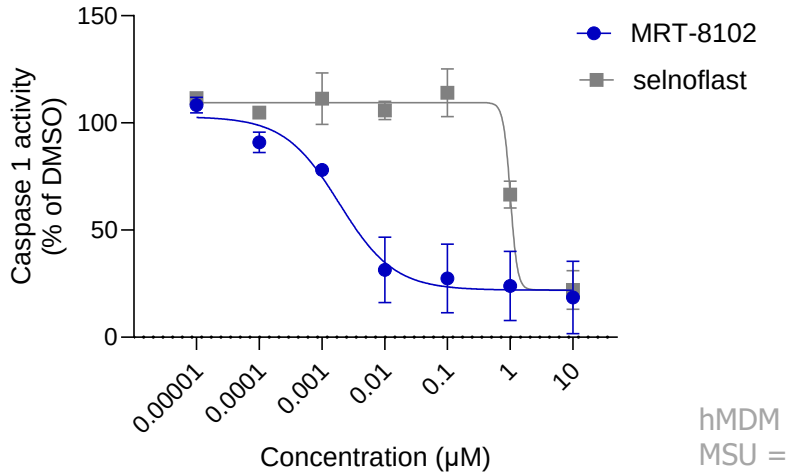
MRT-8102 Inhibits NLRP3 Activation in hMDM Stimulated with MSU/CPPD Crystals and in Whole Blood From Donors Diagnosed with Gout

MRT-8102 reduces Caspase-1 activation by MSU and CPPD crystals in hMDM

MSU Crystals



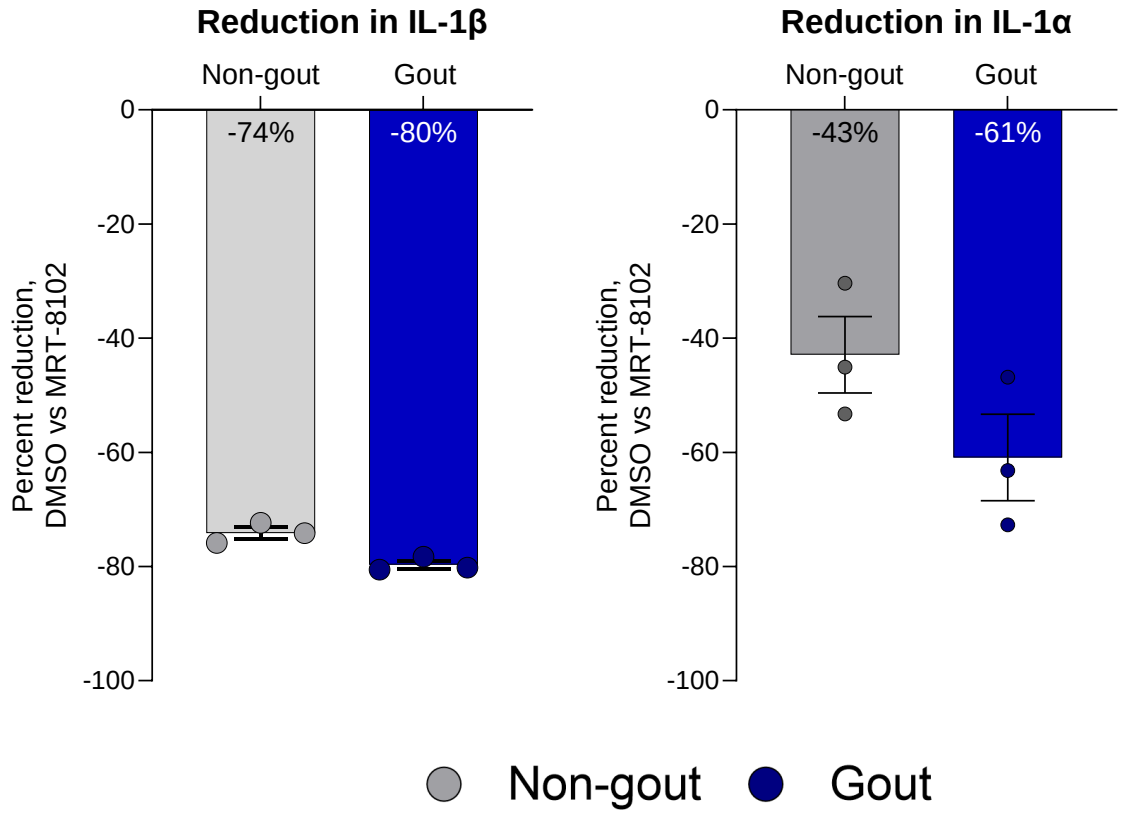
CPPD Crystals



LPS + MSU/CPPD crystals stimulation

MRT-8102 prevents IL-1 release in whole blood from gout and non-gout donors

LPS + Nigericin stimulation



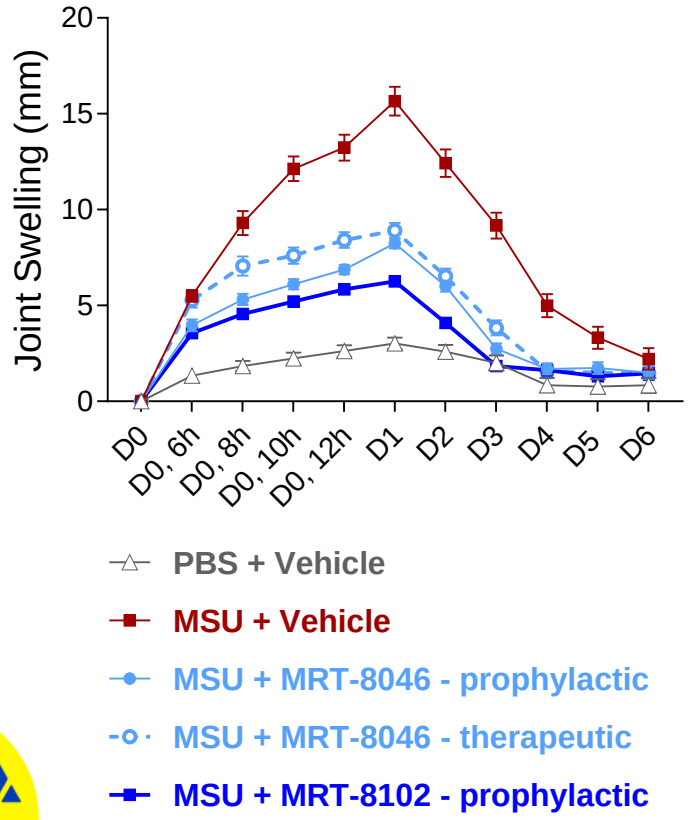
hMDM = human monocyte-derived macrophages
MSU = monosodium urate
CPPD = calcium pyrophosphate dihydrate

Gout diagnosis within 5 years

MRT-8102 Reduced MSU Crystal-driven Effects in Rabbit Gout Model

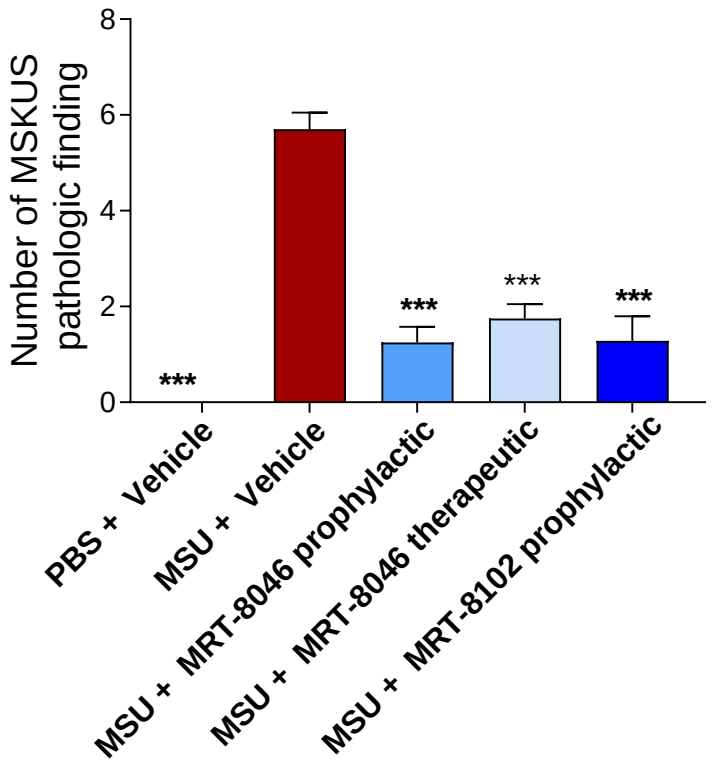
Model developed through single intra-articular injection of MSU (50 mg/kg) in rabbits

Joint swelling



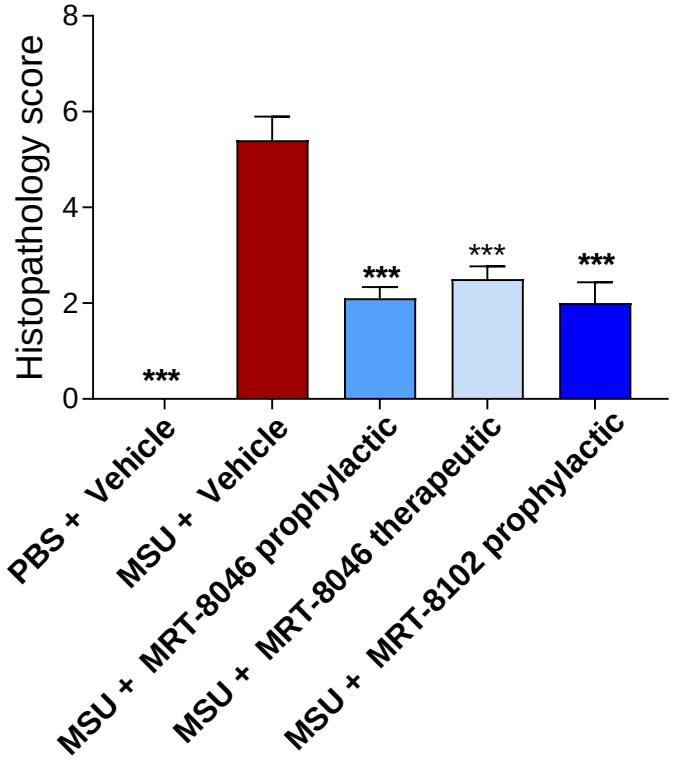
Prophylactic daily dosing from day -1 (prior to MSU)
Therapeutic daily dosing, from day 1 (after MSU)
Intra-articular injection of MSU on day 0
*** denotes $p < 0.0005$ vs. MSU + Vehicle condition

MSKUS pathologic findings



Quantification of musculoskeletal ultrasound (MSKUS):
Global knee distention; synovial fluid, increase in synovial thickening; increase in intra-synovial power-doppler signal

Histopathology score



Histopathology score based on quantification of:
- Enlargement of synovial lining cell layer
- Density of resident cells
- Inflammatory infiltrate

Degradation of NEK7 Using an MGD is a Novel Approach to Targeting IL-1 Through the NLRP3 Inflammasome

- Monte Rosa Therapeutics' molecular glue degrader MRT-8102 is a selective, potent and durable NEK7 degrader.
- MRT-8102 leads to inhibition of the NLRP3 inflammasome *in vitro* and *in vivo*, with therapeutic activity in rabbit gout model.
- MRT-8102 has potential for application in gout and other inflammatory disorders.

Thank You to a Global Team

Boston

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