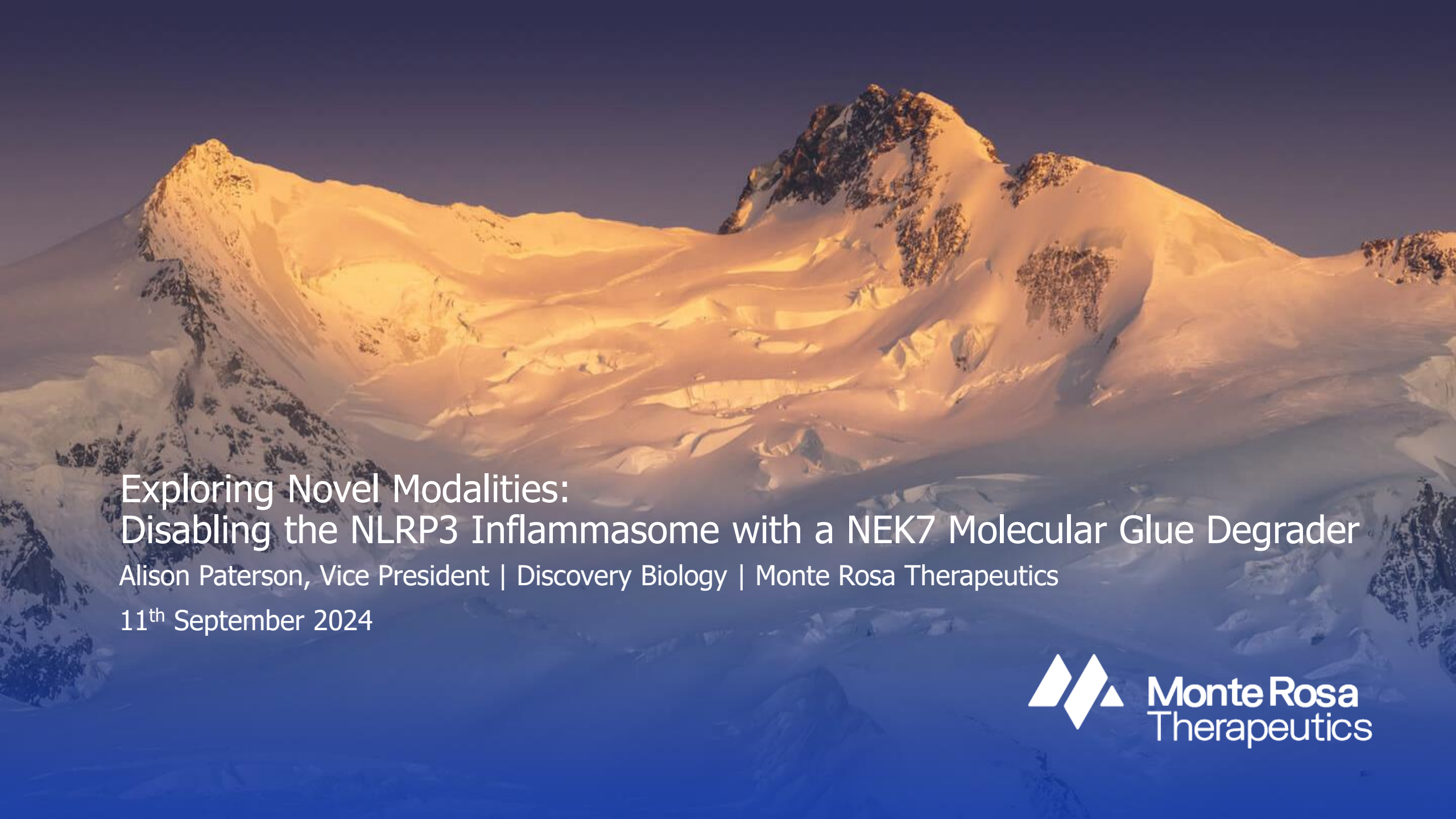

Exploring Novel Modalities: Disabling the NLRP3 Inflammasome with a NEK7 Molecular Glue Degrader

Alison Paterson, Vice President | Discovery Biology | Monte Rosa Therapeutics

11th September 2024

Monte Rosa Therapeutics

Forward-looking Statements

This communication includes express and implied "forward-looking statements," including forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements include all statements that are not historical facts and, in some cases, can be identified by terms such as "may," "might," "will," "could," "would," "should," "expect," "intend," "plan," "objective," "anticipate," "believe," "estimate," "predict," "potential," "continue," "ongoing," or the negative of these terms, or other comparable terminology intended to identify statements about the future. Forward-looking statements contained herein include, but are not limited to, statements about the ongoing development of our NEK7-directed MGD, referred to as MRT-8102, and our expectations around its potential across neurologic indications amongst others, as well as potential use in gout, pericarditis, and other peripheral inflammatory conditions, including our expectations to submit an IND to the FDA in the first quarter of 2025, and our statements around multiple anticipated clinical readouts, including results from proof-of-concept patient studies for MRT-8102, statements around the advancement and application of our platform, statements concerning our expectations regarding our ability to nominate and the timing of our nominations of additional targets, product candidates, and development candidates, statements regarding regulatory filings for our development programs, including the planned timing of such regulatory filings, such as IND applications, and potential review by regulatory authorities, our use of capital, expenses and other financial results in the future, availability of funding for existing programs, ability to fund operations into the first half of 2027, as well as our expectations of success for our programs, strength of collaboration relationships and the strength of our financial position, among others. By their nature, these statements are subject to numerous risks and uncertainties, including those risks and uncertainties set forth in our most recent Annual Report on Form 10-K for the year ended December 31, 2023, filed with the U.S. Securities and Exchange Commission on March 14, 2024, and any subsequent filings, that could cause actual results, performance or achievement to differ materially and adversely from those anticipated or implied in the statements. You should not rely upon forward-looking statements as predictions of future events. Although our management believes that the expectations reflected in our statements are reasonable, we cannot guarantee that the future results, performance, or events and circumstances described in the forward-looking statements will be achieved or occur. Recipients are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date such statements are made and should not be construed as statements of fact. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, any future presentations, or otherwise, except as required by applicable law. Certain information contained in these materials and any statements made orally during any presentation of these materials that relate to the materials or are based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party studies, publications, surveys and other data to be reliable as of the date of these materials, we have not independently verified, and make no representations as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, no independent source has evaluated the reasonableness or accuracy of our internal estimates or research and no reliance should be made on any information or statements made in these materials relating to or based on such internal estimates and research.

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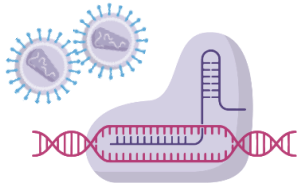
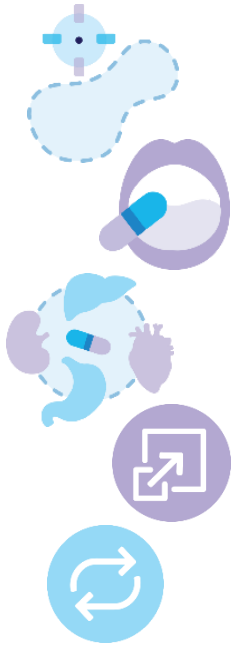
An Introduction to Molecular Glue Degraders at Monte Rosa Therapeutics

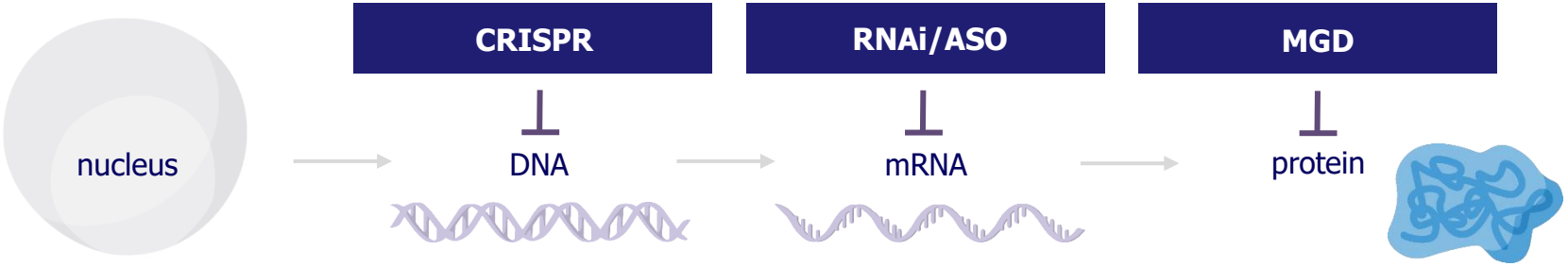
Molecular Glue Degraders (MGDs) – A Highly Differentiated Modality

Advantages of large molecule modalities with orally dosed small molecules

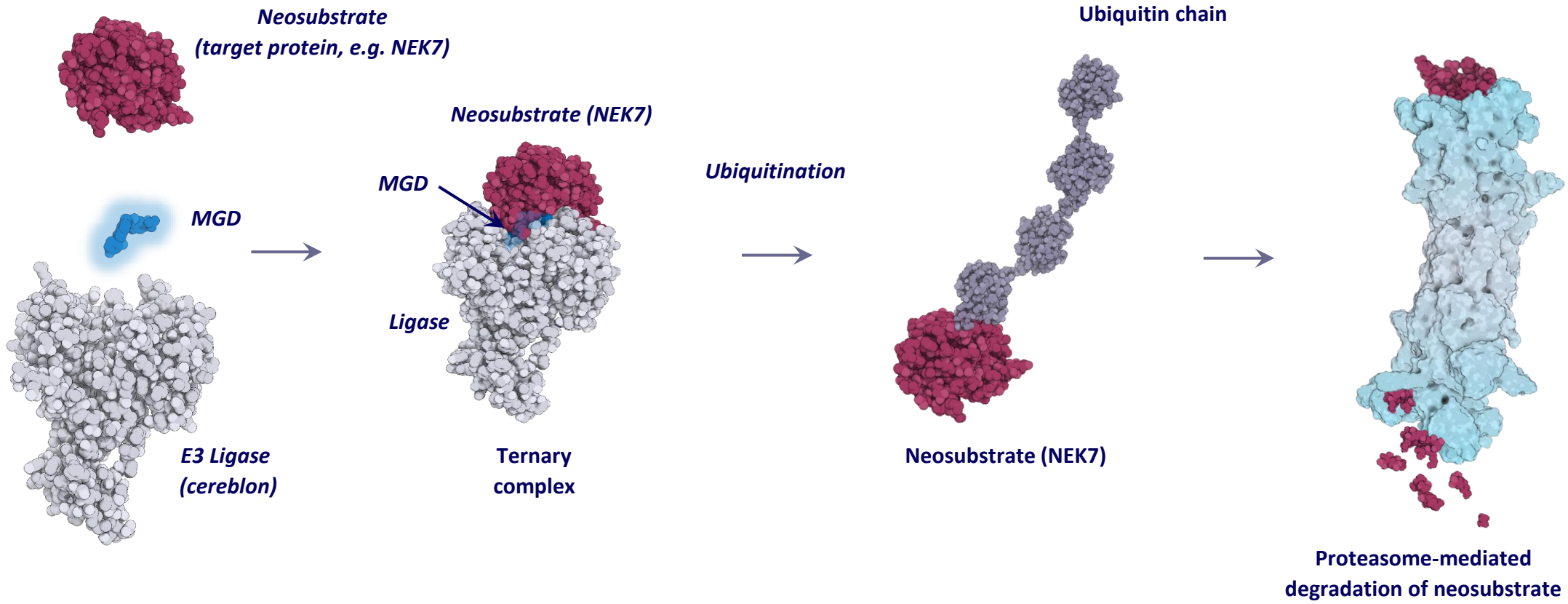


Properties	CRISPR	RNAi/ASO	MGD
Address undruggable space	✓	✓	✓
Orally bioavailable			✓
Systemic distribution			✓
Scalable manufacturing			✓
Reversible		✓	✓





Our Molecular Glue Degraders (MGDs) Edit the Proteome



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

Monte Rosa Pipeline and Upcoming Milestones

Target	Compound	Indication(s)	Discovery	IND-Enabling	Clinical	Next Anticipated Milestone	Ownership
GSPT1	MRT-2359	NSCLC, SCLC and other MYC-driven Malignancies				RP2D and Phase 1 data in H2 2024	
VAV1	MRT-6160	Autoimmune Disease – Systemic and CNS				Phase 1 data in Q1 2025	
NEK7	MRT-8102	IL-1β/NLRP3-driven Inflammatory Diseases				IND submission in H1 2025	
	LO (2nd generation)					Development candidate	
CDK2	LO	Breast Cancer				Development candidate in 2024	
CCNE1 (Cyclin E1)	LO	CCNE1 amplified tumors				Development candidate	
Discovery Targets	-	Multiple				Lead optimization	
Discovery Targets	-	Oncology and Neurological Diseases				Undisclosed	Roche

Oncology Immunology Inflammation Various

As presented in company disclosures, August 19, 2024

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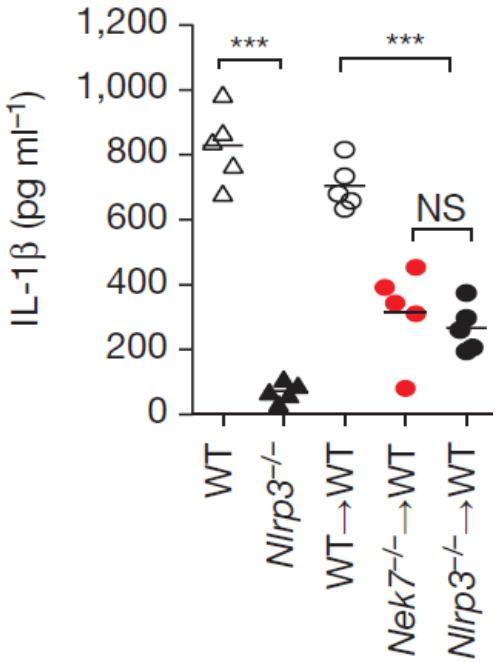
NEK7 as a Critical Component of NLRP3 Inflammasome

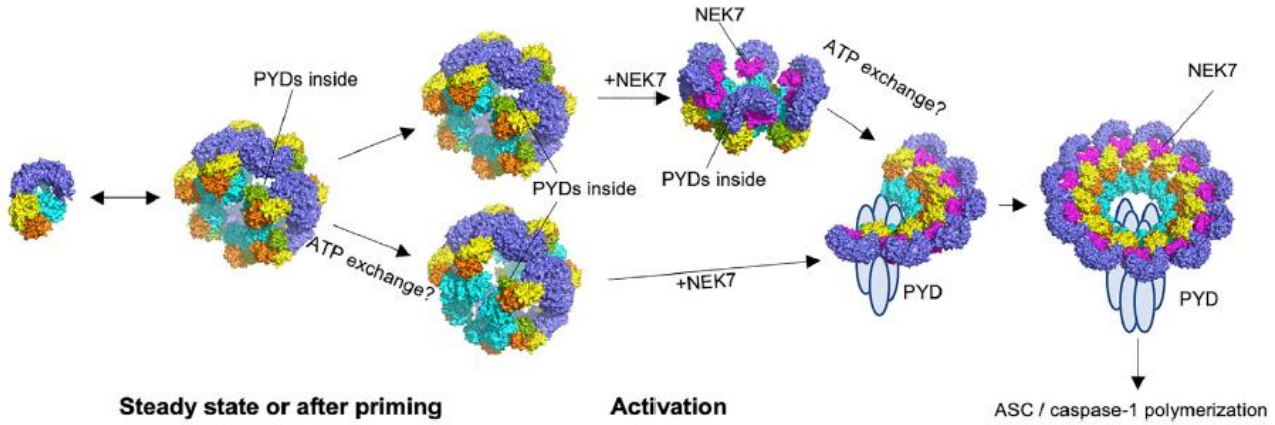
Connecting NEK7 to the NLRP3 Inflammasome – The History

NEK7 is required for activation of the NLRP3 inflammasome *in vivo*



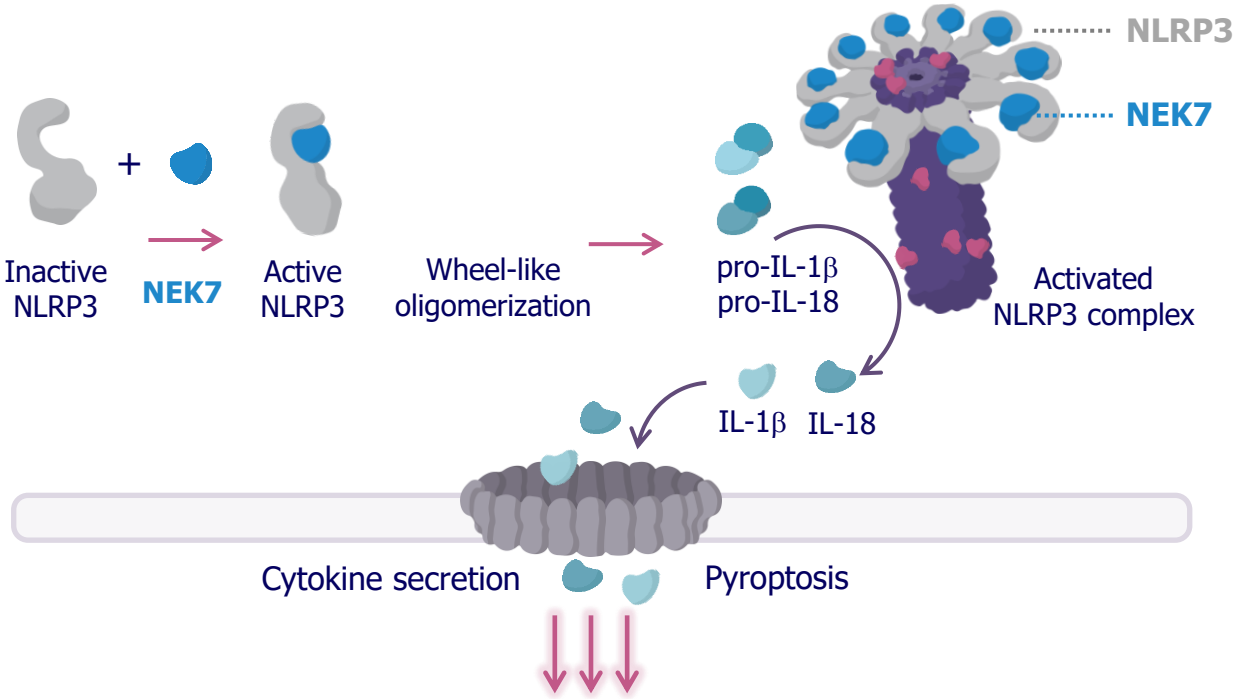
He et al., Nature 2016

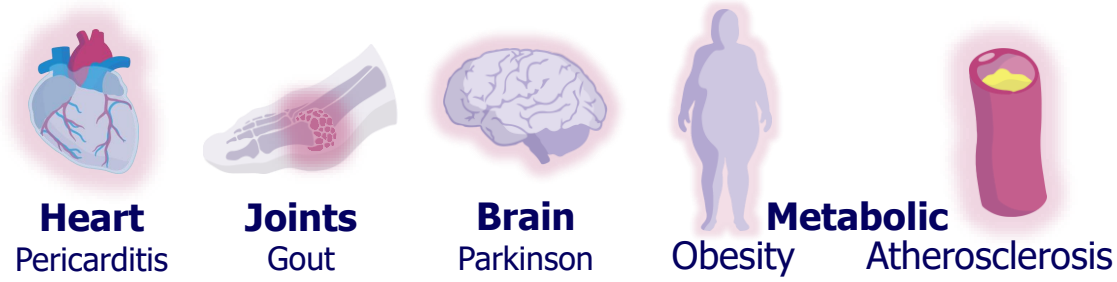
Structural licensing of NLRP3 by NEK7 binding



Andreeva et al., Cell 2021

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





Therapeutic Hypothesis:

Activation of the NLRP3 inflammasome critically depends on NEK7

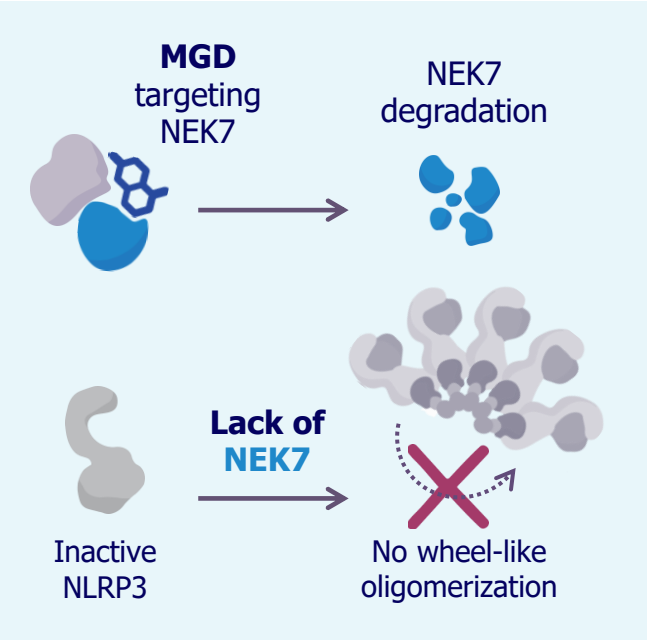
- NEK7 licenses NLRP3 assembly in a kinase-independent manner
- NEK7-deficient macrophages are severely impaired in IL-1β and IL-18 secretion

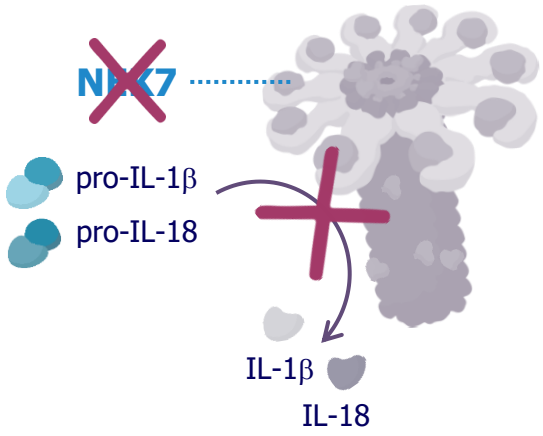
Consequently, NEK7 degradation has the potential to become an important treatment modality for a variety of inflammatory diseases

Clinical Opportunity:

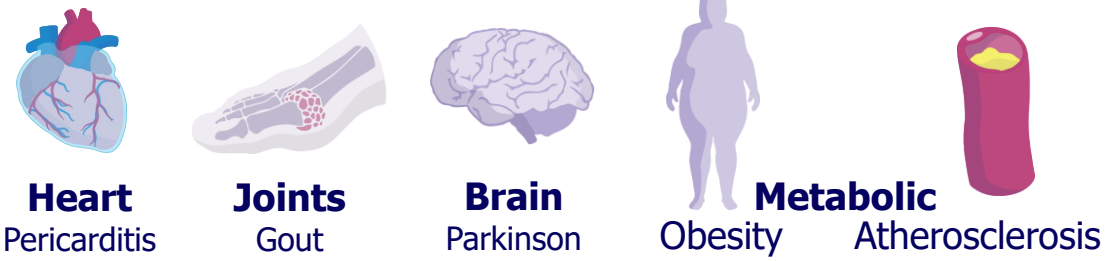
Diseases driven by IL-1 and the NLRP3 inflammasome including gout, pericarditis and other cardiovascular disease, neurodegenerative disease, and obesity

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





Dysfunctional NLRP3 inflammasome



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Clinical Opportunity:

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The Evolving NLRP3 Modulator Landscape

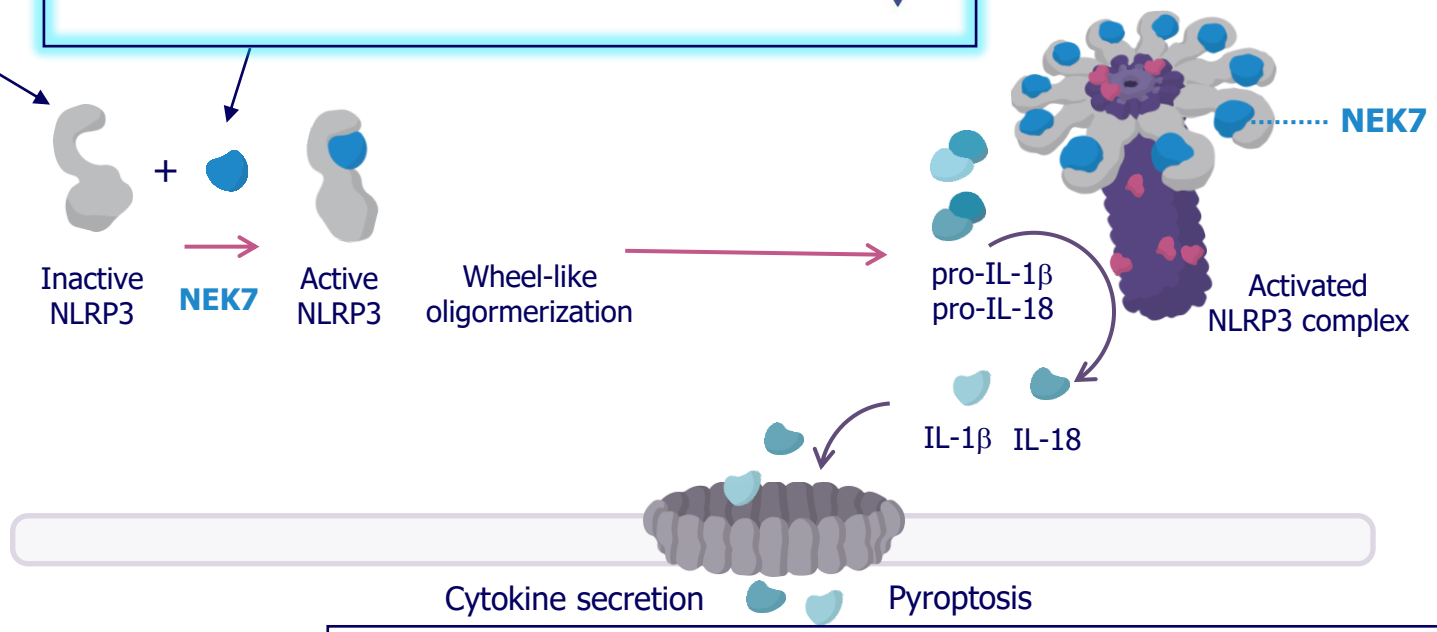
Small molecule inhibitors targeting NLRP3
- Multiple programs with limited chemical space

MGD targeting NEK7

NEK7 degradation

- Novel chemical space
- Potent
- Selective
- Durable

INVESTIGATIONAL UPSTREAM AGENTS
- Oral administration



APPROVED DOWNSTREAM BIOLOGICS
- Injectable

Rilonacept (neutralizing IL-1α and IL-1β)

Canakinumab (neutralizing IL-1β)

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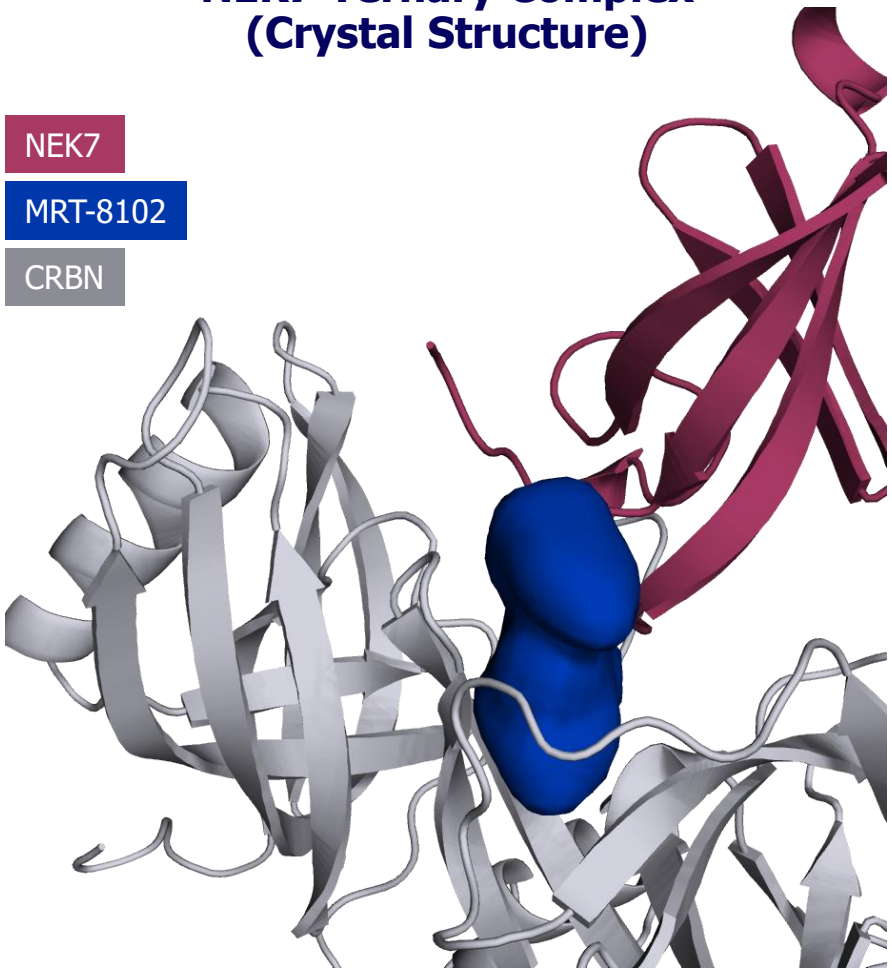
NEK7 MGD – MRT-8102

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

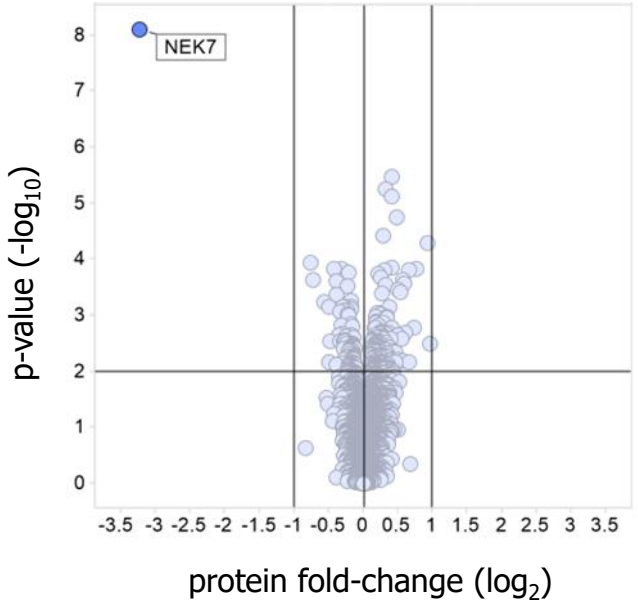
NEK7 Ternary Complex (Crystal Structure)



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

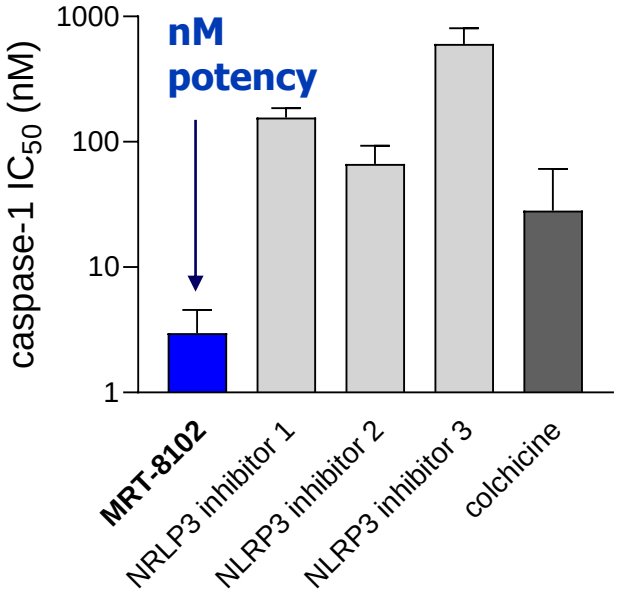
NEK7 MGD as a Differentiated Approach to Targeting NLRP3 Inflammasome

Selectivity



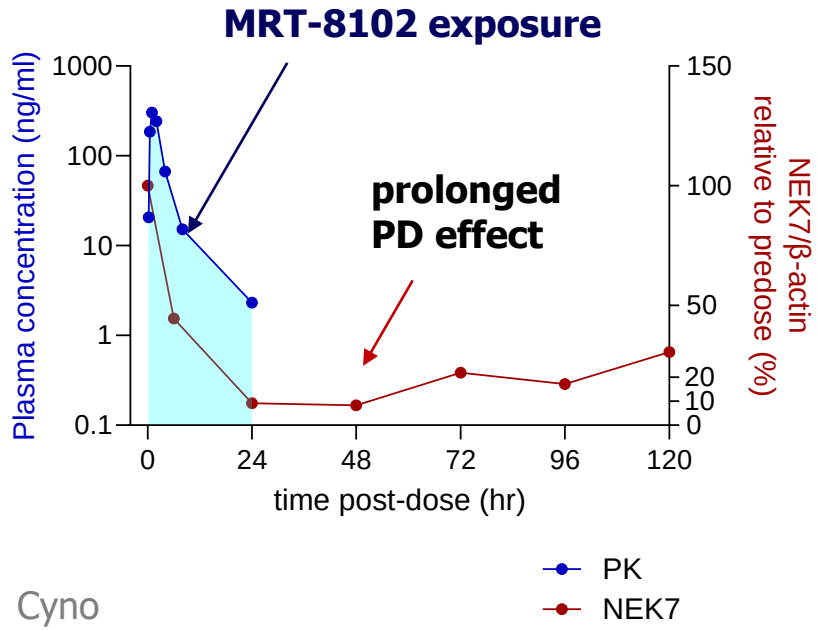
hPBMC

Potency



hMDM

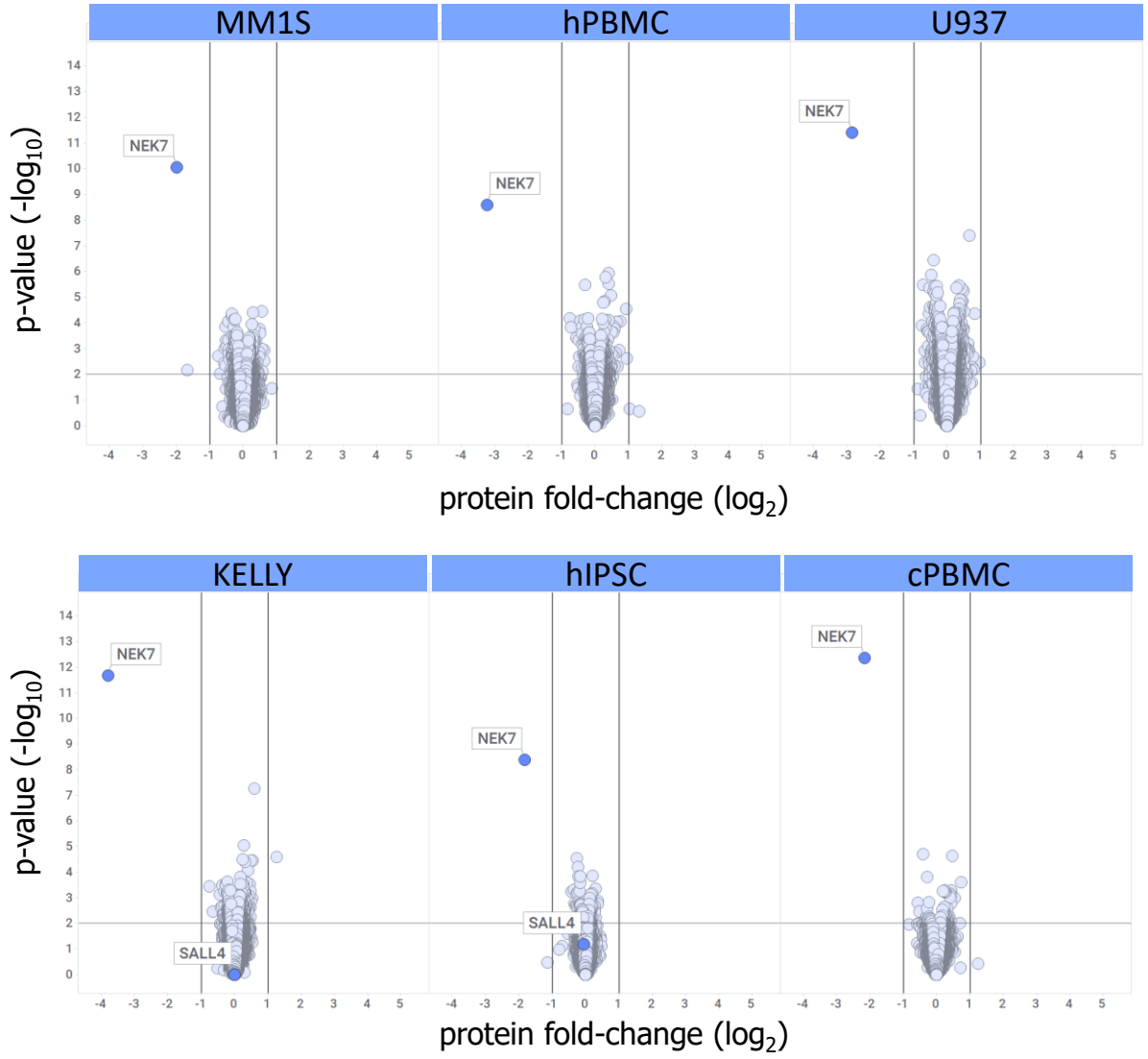
Durability



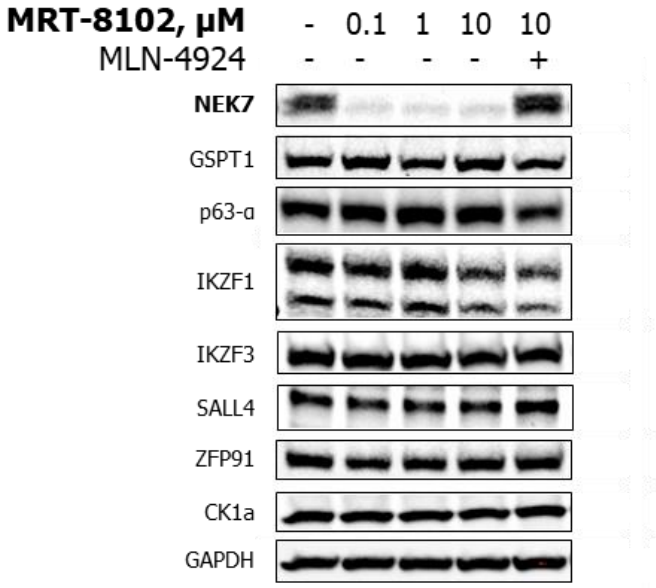
Cyno
10 mg/kg single-dose

hMDM = human monocyte-derived macrophages
hPBMC = human peripheral blood mononuclear cells
cyno = cynomolgus monkey

MRT-8102 is Highly Selectivity Across a Broad Array of Cells



MRT-8102 at 10 µM in each cell line, 24h

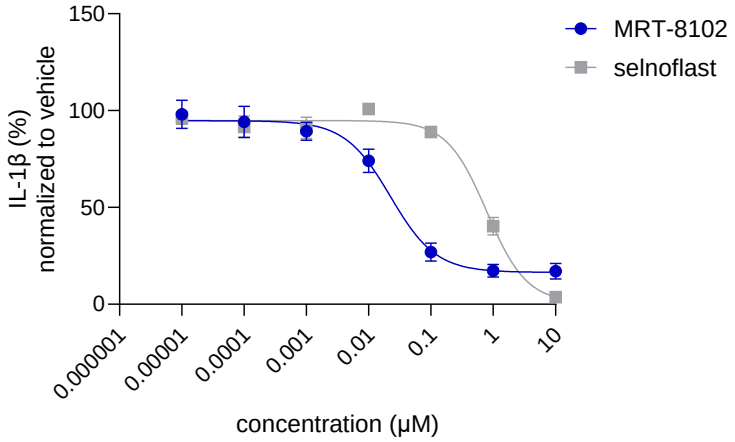


6h post treatment in MM.1S, Kelly (SALL4), or Raji (p63-α)
2uM MLN-4924, 30 min pre-treatment

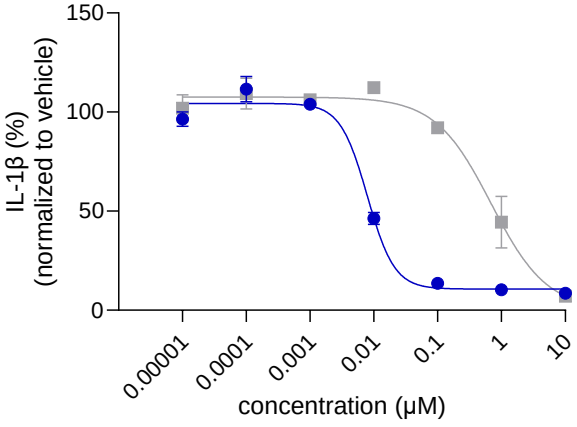
MRT-8102 Leads to Potent Inhibition of NLRP3 Inflammasome in Human and Cynomolgus Monkey Cells *In Vitro*

Reduced IL-1β in human and cynomolgus monkey whole blood

Human

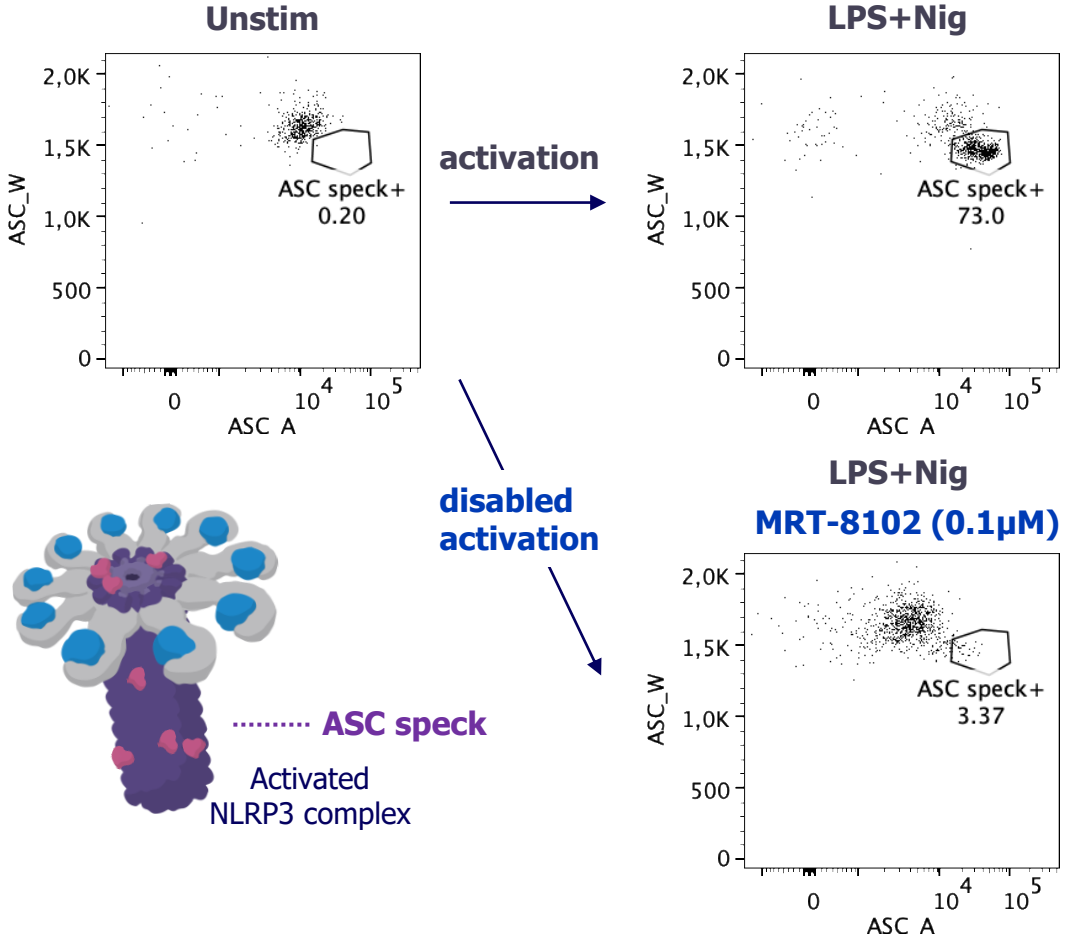


Cyno



LPS + Nigericin

Reduced ASC speck formation in human whole blood

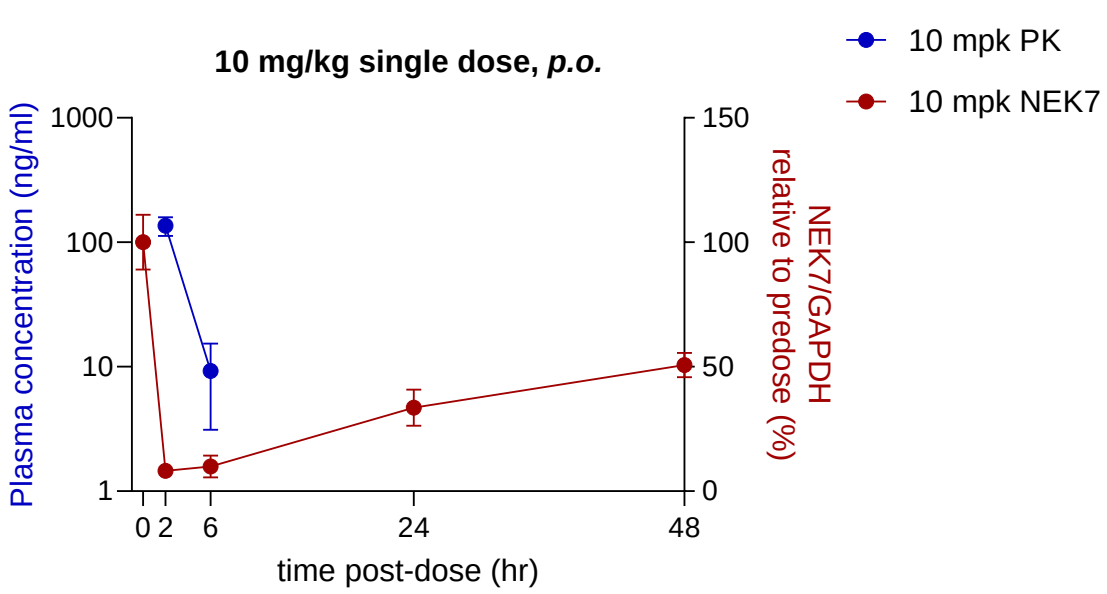


Gating strategy: Single cells_CD45+_CD66b-_CD14+

MRT-8102 Degrades NEK7 in Single-Dose *in vivo* Studies

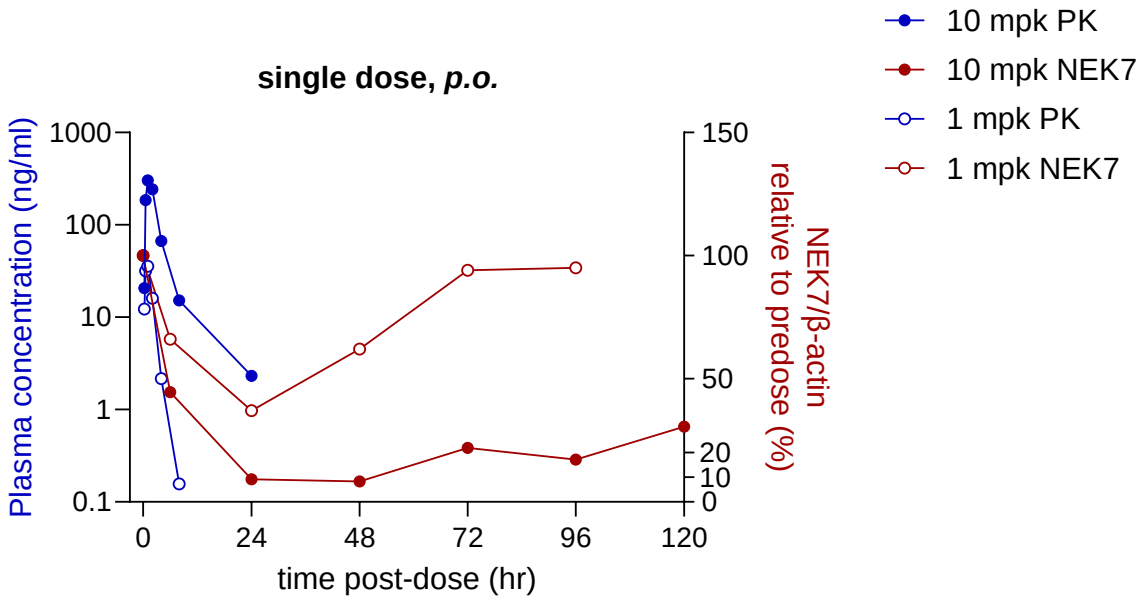
MRT-8102 does not degrade NEK7 in rodent species; PK/PD models in xenograft and cyno

MRT-8102 shows deep degradation in U937 xenograft PK/PD model



U937 s.c. xenograft
n=3 CB17.SCID mice per timepoint
hNEK7 levels in U937 tumor

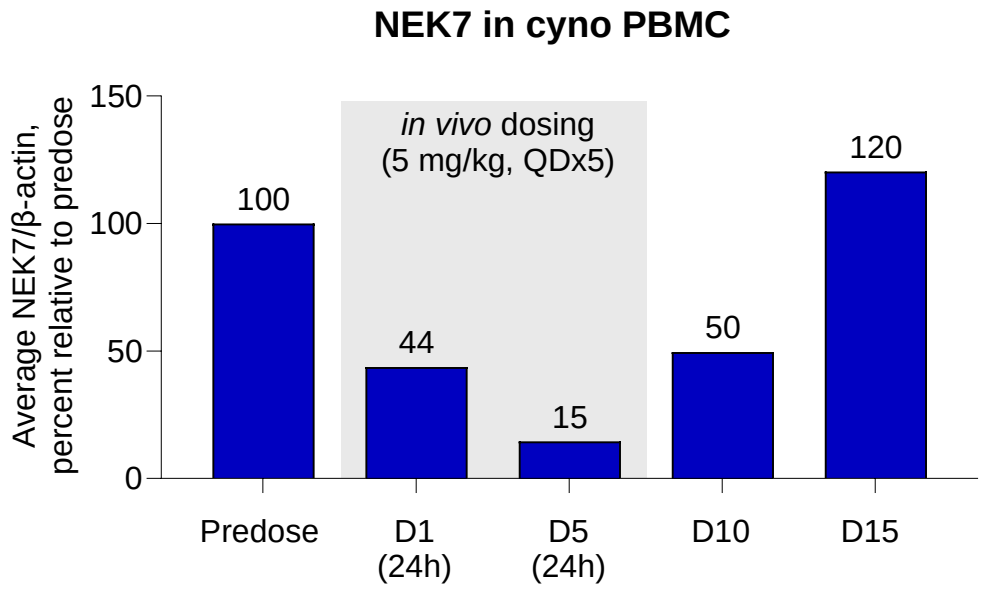
MRT-8102 shows dose-dependent degradation in cynomolgus monkey



n=2 cynomolgus monkey (one male and one female) per dose
cNEK7 levels in PBMC

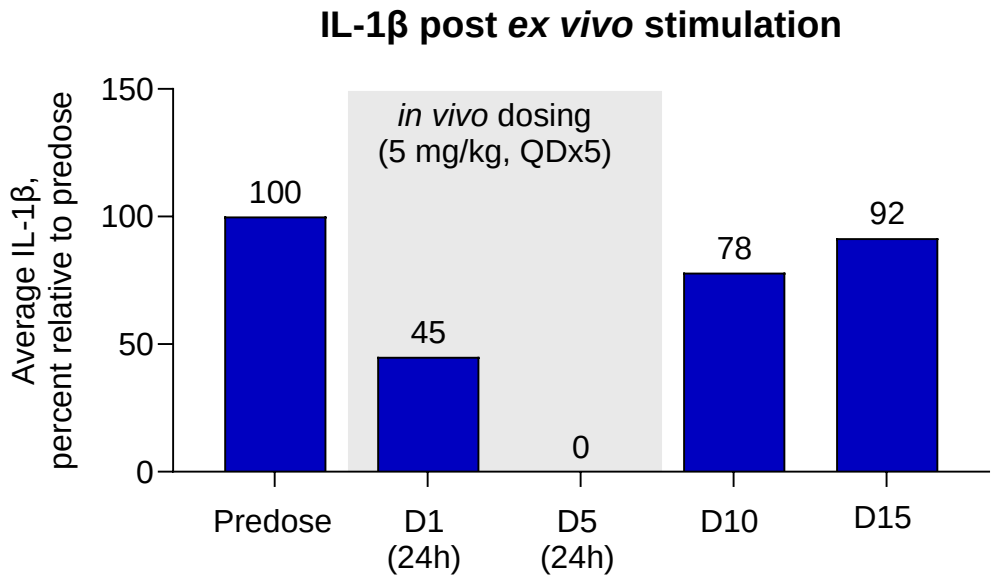
In Vivo Proof-of-mechanism for NEK7 MGD MRT-8102

MRT-8102 induces degradation of NEK7 *in vivo* over several days



n = 2

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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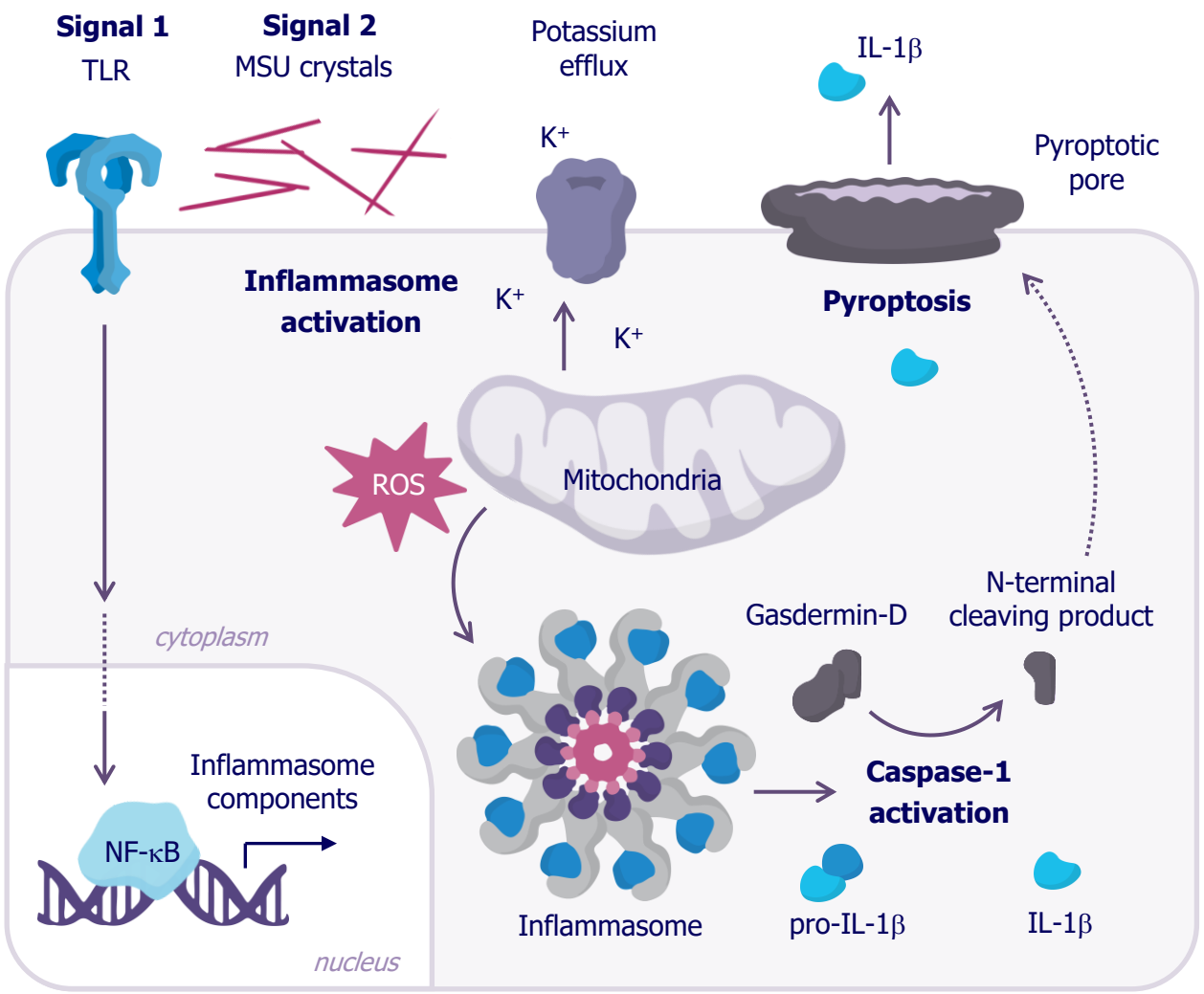
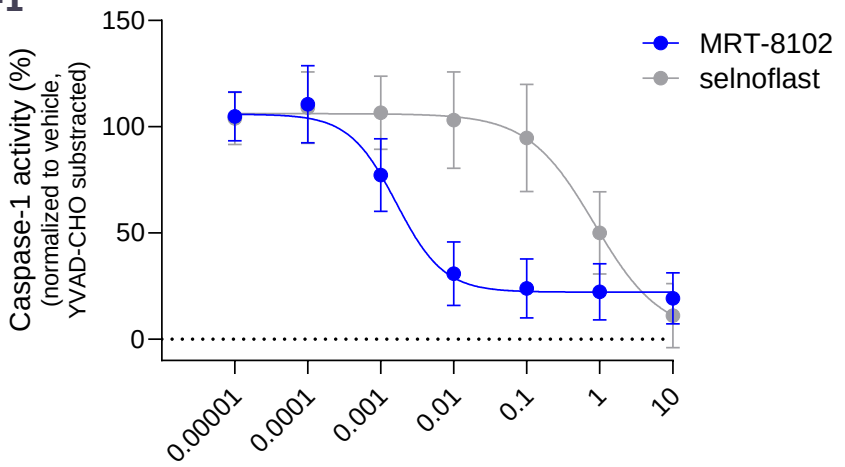
Gout as a Clinical Opportunity

NEK7 MGDs Inhibit NLRP3 Activation by Monosodium Urate

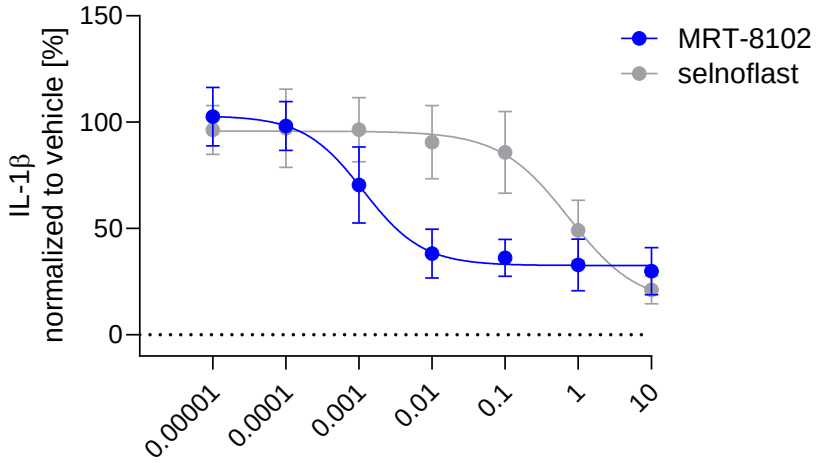


MRT-8102 reduces MSU-induced NLRP3 inflammasome activation

Caspase-1



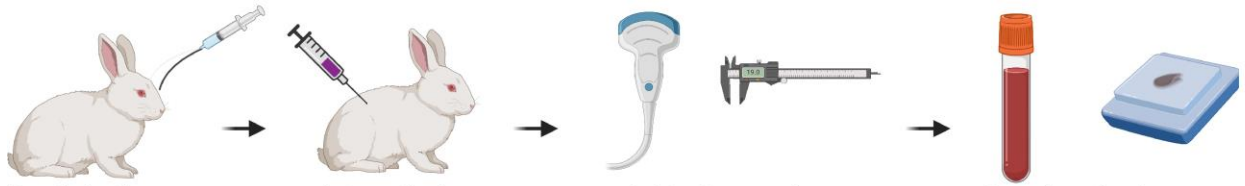
IL-1β



Human monocyte-derived macrophages LPS + MSU stimulation
Pretreatment with molecular glue degrader (MGD) or NLRP3 inhibitor (NLRP3i)

NEK7 MGD Reduces MSU-Driven Effects In Rabbit Gout Model

MRT-8046 is rabbit-active NEK7 MGD



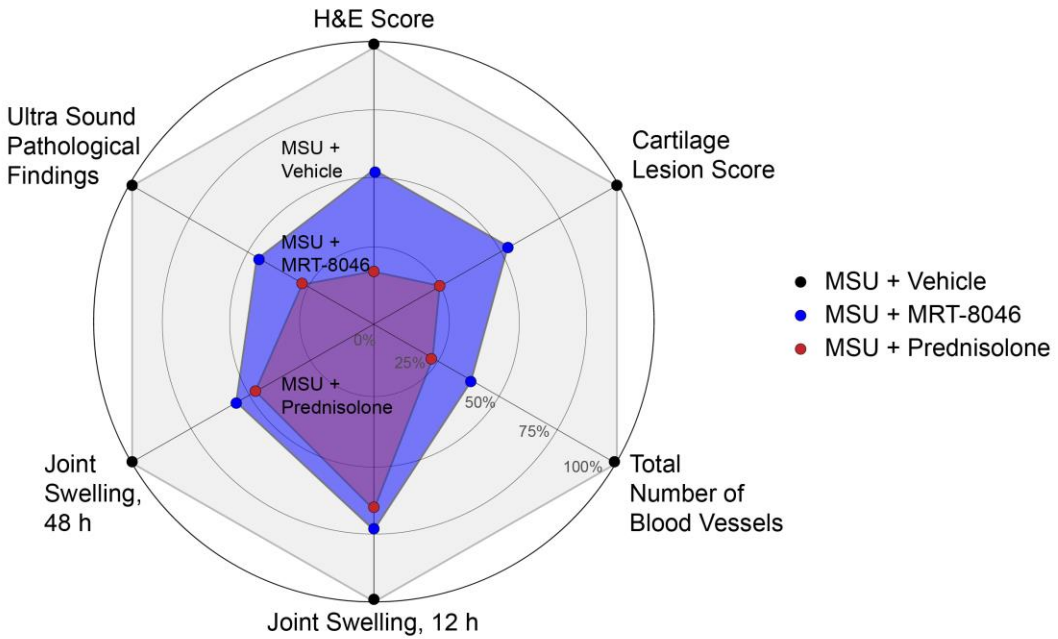
Prophylactic daily dosing of MRT-8046 or Prednisolone, *day -1*

Intra-articular injection of MSU, *day 0*

Joint ultrasound and caliper measurements, *days 0-7*

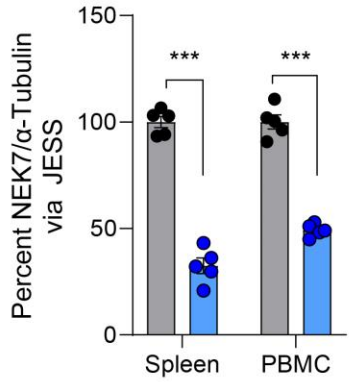
Sample collection (PBMCs & histology), *day 7*

Pathological Findings, Relative to MSU + Vehicle Condition

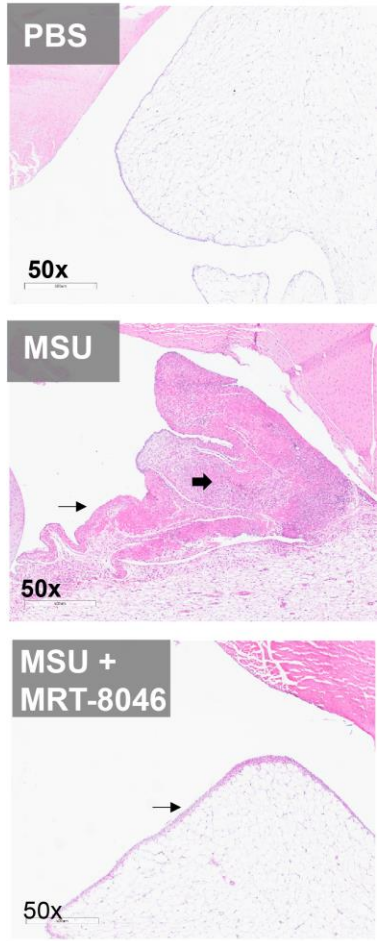


Reduced area correlates with improved response

NEK7 Protein



Samples harvested 2h post final dose



→ Hyperplastic lining layer of the synovial membrane

➡ Inflammatory cell infiltration

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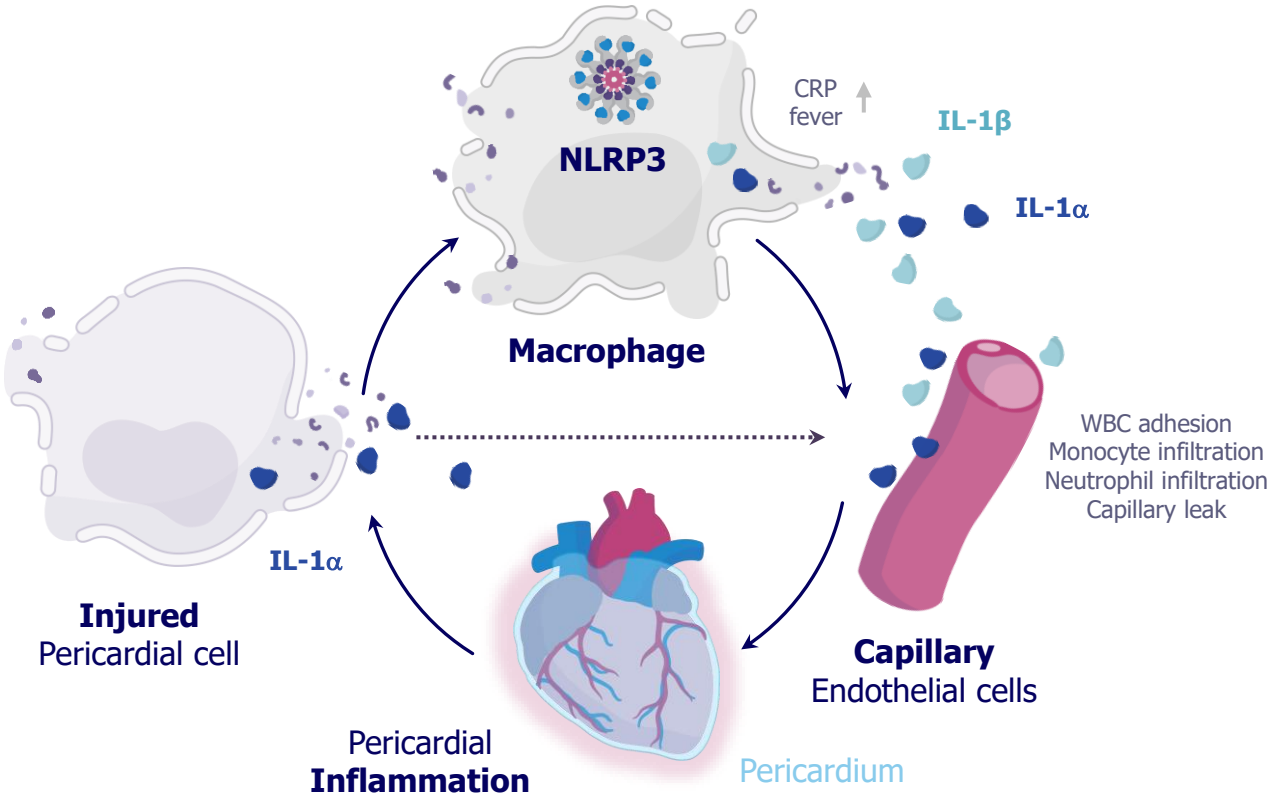
Pericarditis as a Clinical Opportunity

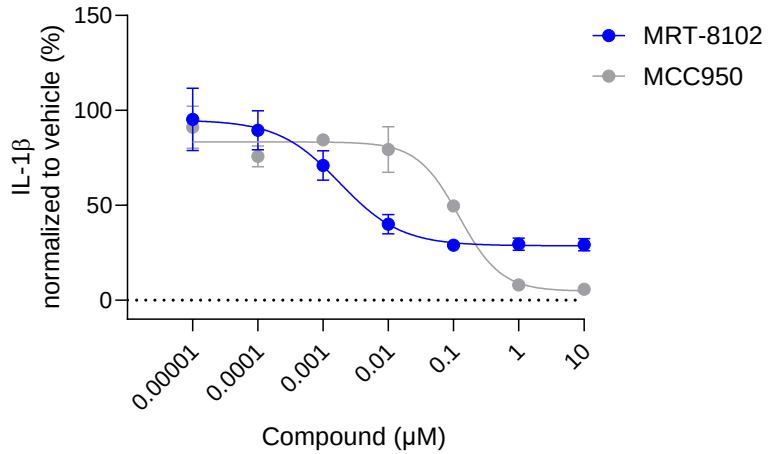
The IL-1 Pathway is Clinically Validated in Pericarditis



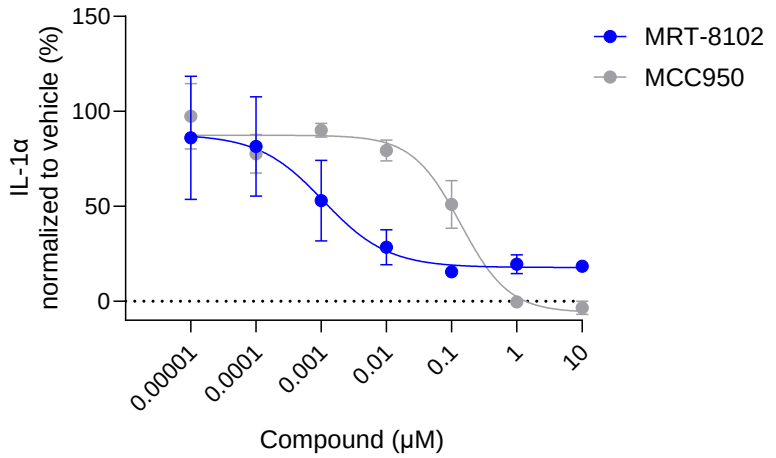
- IL-1β, downstream of NLRP3 activation, amplifies inflammatory cycle
- Colchicine is first line therapy
- Rilonacept approved; oral alternatives required

MRT-8102 inhibits release of both IL-1β and IL-1α in pyroptosis assay

IL-1β



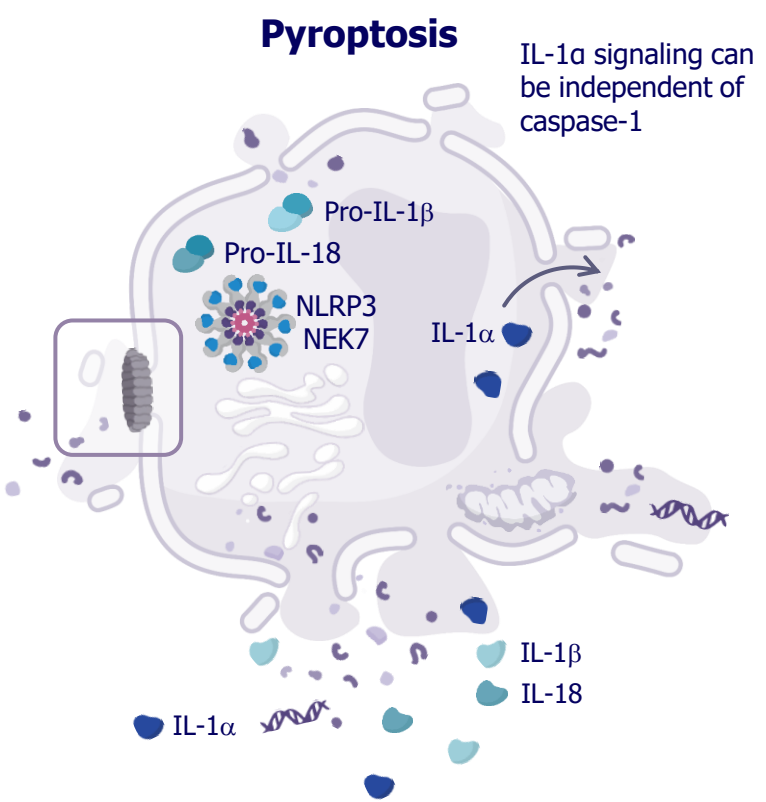
IL-1α



Human monocyte-derived macrophages LPS + Nigericin stimulation
Pretreatment with molecular glue degrader (MGD) or NLRP3 inhibitor (NLRP3i)

NEK7 MGD Has Potential to Resolve Inflammation by Inhibiting Pyroptosis

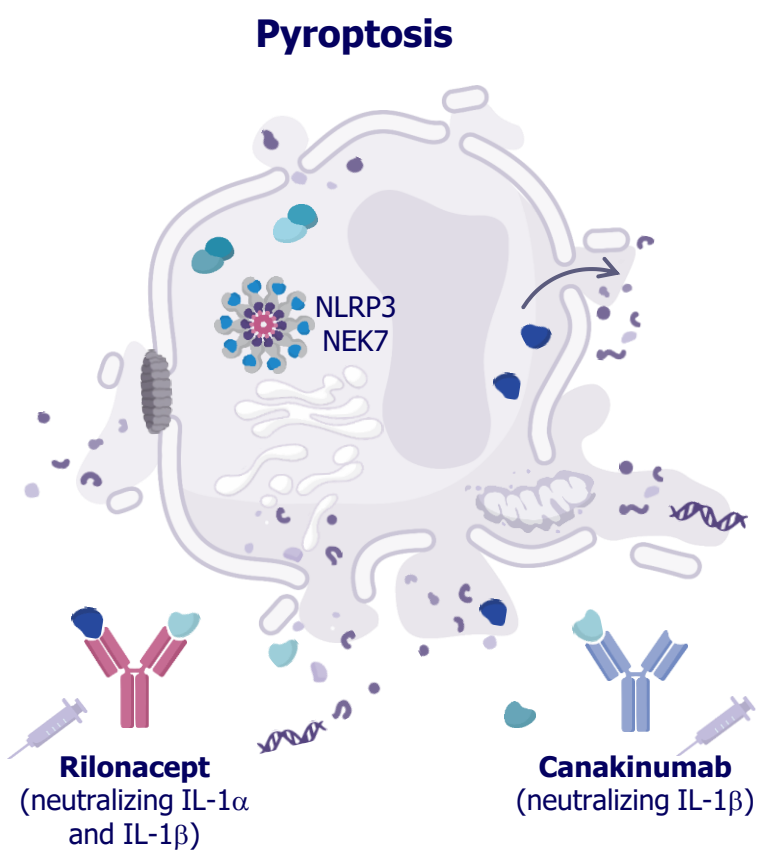
NLRP3/NEK7-driven inflammation



Release of DAMPS, nucleic acids, alarmins, inflammatory cytokines

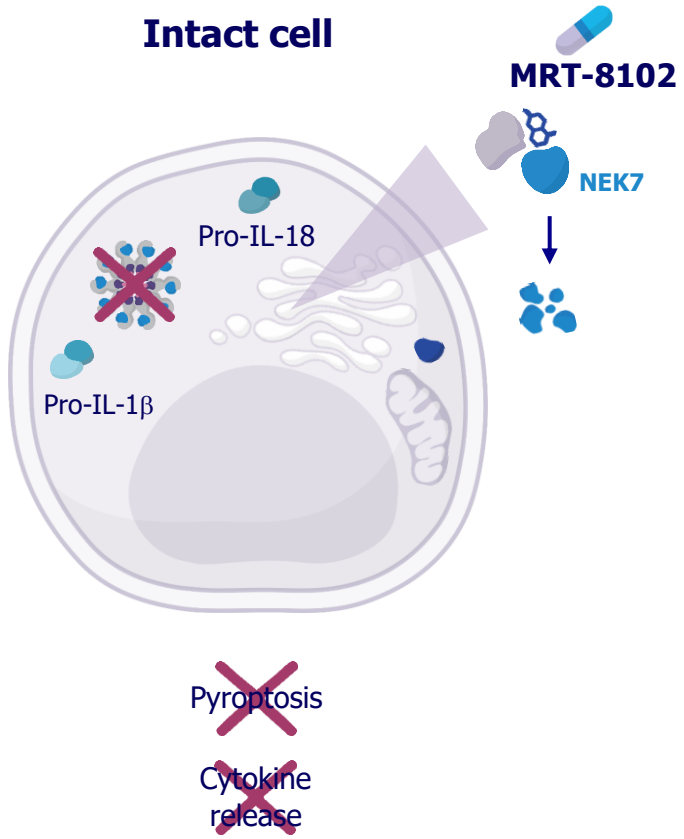
Full inflammation

Inhibition of IL-1 driven inflammation



Reduced inflammation

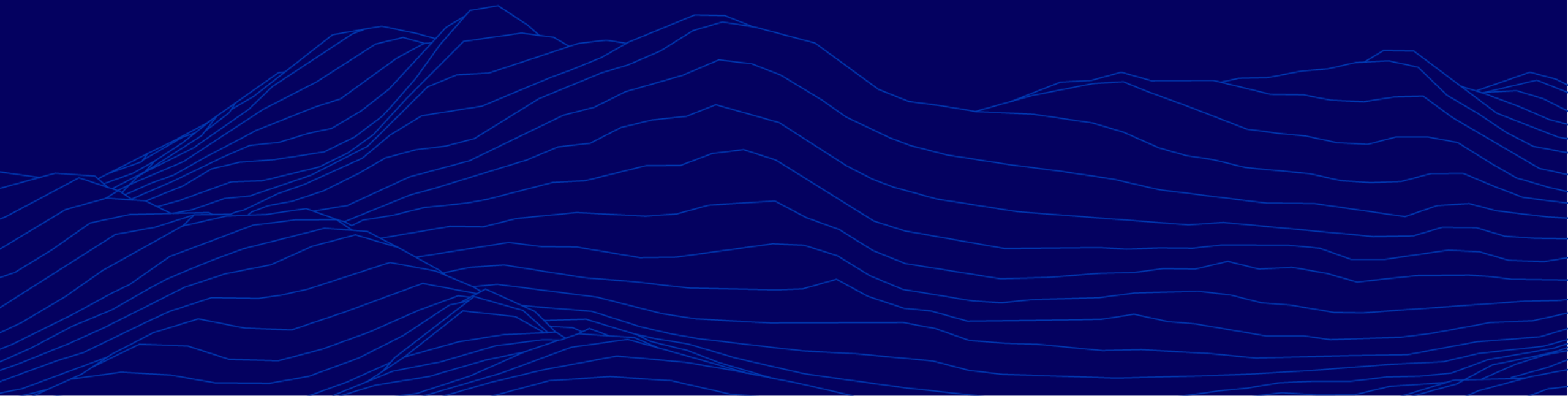
Resolution of inflammation with NEK7 MGD



Aborted inflammation

Monte Rosa Therapeutics

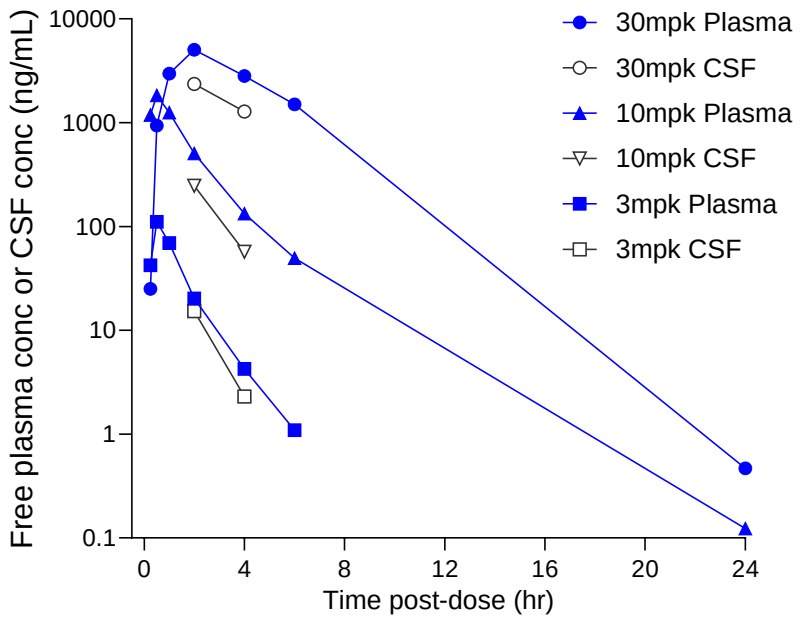
Future Opportunities



MRT-8102 Displays Blood-brain Barrier Penetration in Cynomolgus Monkey

MRT-8102 displays CNS-penetrance in cynomolgus monkey

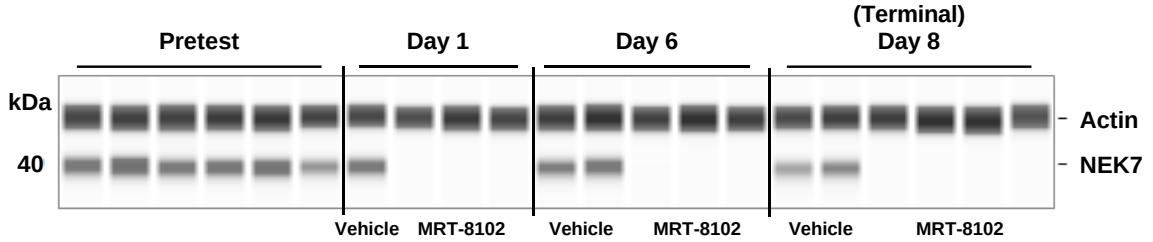
Single dose p.o.



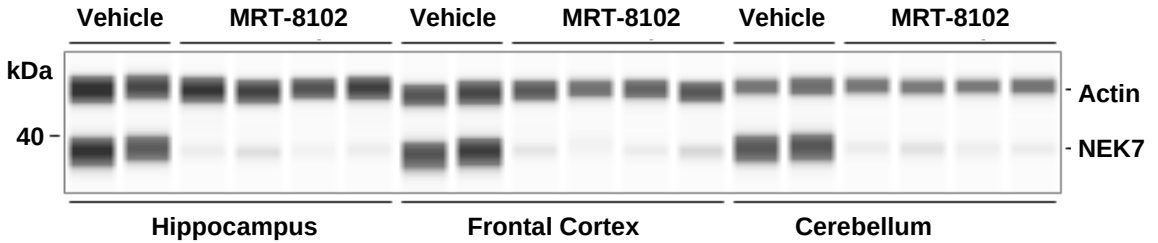
Single-dose MRT-8102 p.o.
n=2 cynomolgus monkey (one male and one female)

Significant NEK7 degradation in various cyno brain regions 24h post treatment

PBMCs



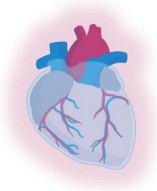
Brain



Daily dose of 30 mg/kg MRT-8102 for 7 days
Analysis on day 8 (24 hr post-final dose) by JESS Simple Western

NLRP3/NEK7 Involvement in a Broad Range of Inflammatory Diseases

Potential for groundbreaking approaches to intractable medical problems



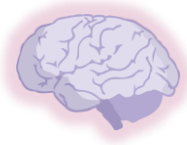
Immuno-cardiology

Treatment + prevention of recurrent pericarditis

Treatment + prevention of acute myocardial infarction

Treatment of myocarditis

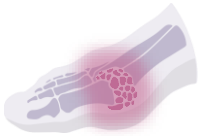
Prevention of heart failure



Neuro-immunology

Treatment of Parkinson's disease

Treatment of Alzheimer's disease



Rheumatology

Treatment + prevention of acute gouty arthritis

Metabolism

Treatment + prevention of obesity

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
- NEK7 MGD leads to inhibition of NLRP3 inflammasome *in vitro* and *in vivo;* therapeutic activity in rabbit gout model
- Potential for broad application in inflammatory disorders; NEK7 MGDs with different tissue distribution could address central as well as peripheral inflammatory disorders

Thank You to a Global Team

Boston

Basel