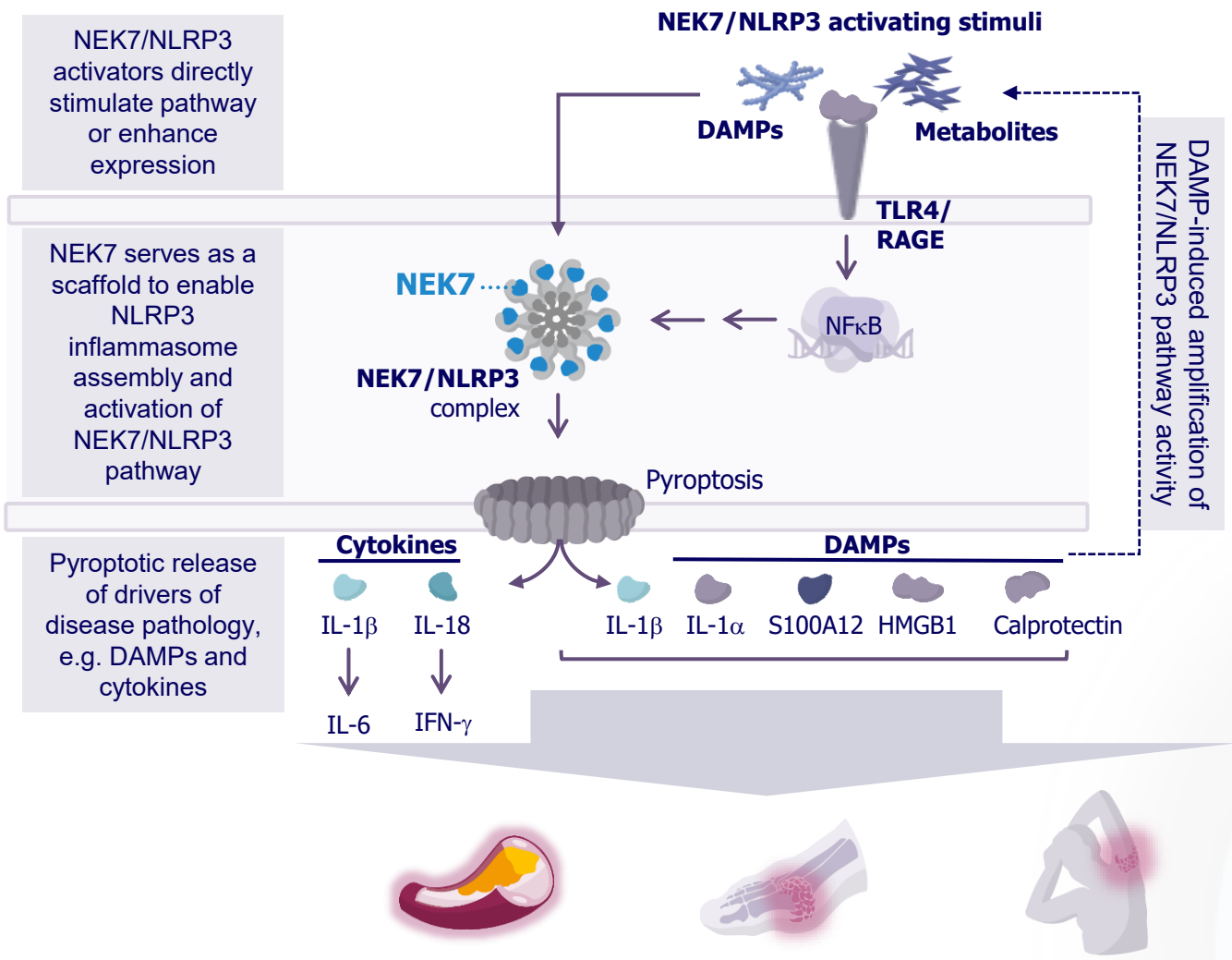


NEK7 Degradation Using MRT-51126, a Selective Molecular Glue Degrader, Induces Weight Loss in Mouse and Cynomolgus Monkey Models of Obesity

Alison Paterson, DPhil
Monte Rosa Therapeutics

NEK7: An Upstream Target to Address NLRP3-Driven Inflammatory Diseases

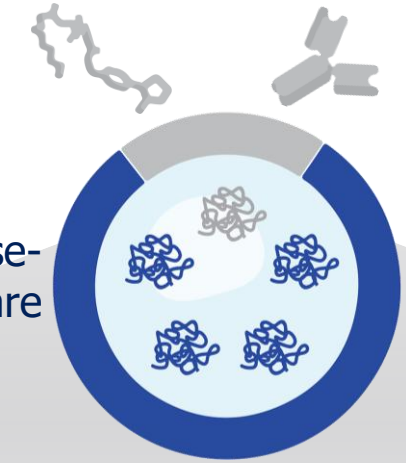


- NEK7 enables NLRP3 inflammasome assembly in a kinase-independent manner
- NLRP3 inflammasome activation causes pyroptotic cell death, causing release of **IL-1α/β**, **IL-18, and damage-associated molecular patterns (DAMPs)**
- **NEK7 degradation** has the potential to become an important treatment for **inflammation-driven diseases** by inhibiting all aspects of NLRP3-driven inflammation
- Targeting of IL-1/NLRP3 **pathway is clinically validated** for inflammatory diseases
  - recurrent pericarditis
  - Gout, rheumatoid arthritis
  - CAPS + autoinflammatory syndromes
  - reduction in cardiac events (CANTOS)
  - hidradenitis suppurativa (Ph3)
  - Many others under investigation

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Molecular Glue Degraders as Paradigm-Shifting Oral Therapeutics

Most disease-causing proteins are **undrugged** with conventional modalities



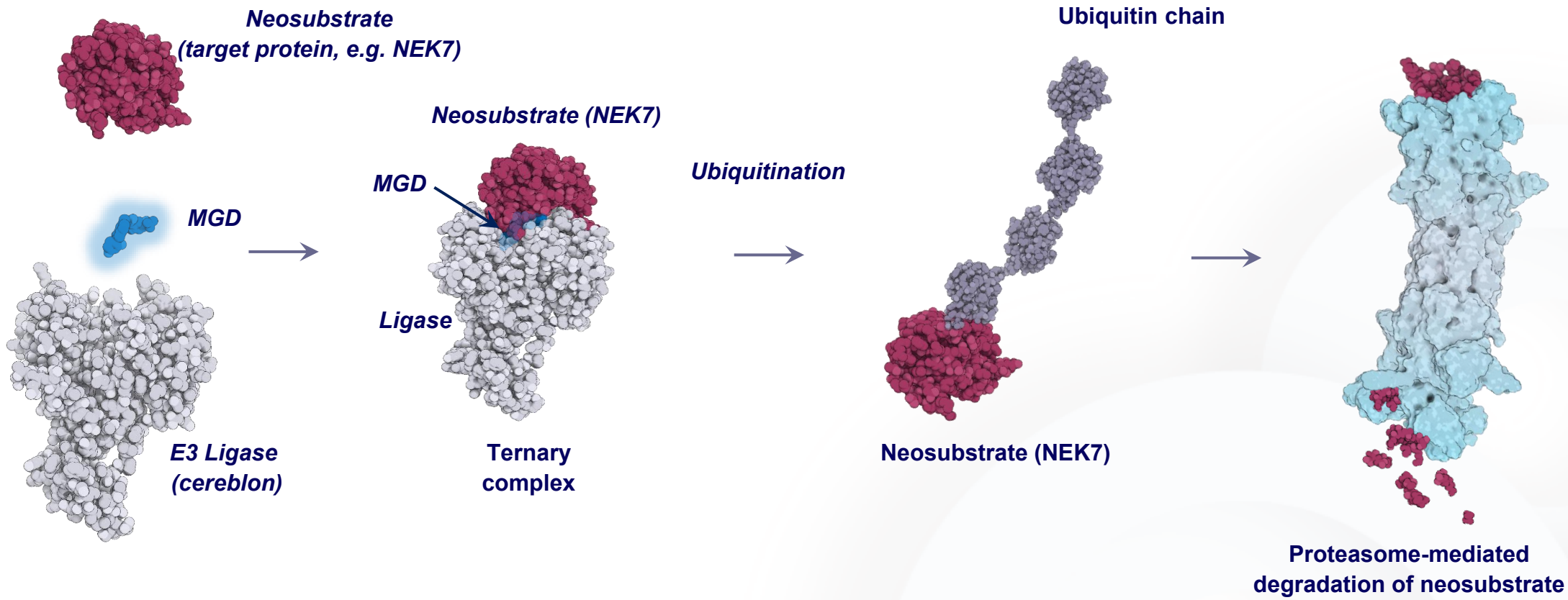
MGDs

- **Clinically validated modality**
- **Exquisite selectivity**
- **Novel target space**
- **Catalytic mechanism of action**
- **Oral dosing**
- **Scalable manufacturing**

Like RNAi and CRISPR, Monte Rosa's **MGDs** have the potential to unlock **undruggable target space** but with the **advantages of oral small molecules**

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Molecular Glue Degraders (MGDs) Edit the Proteome

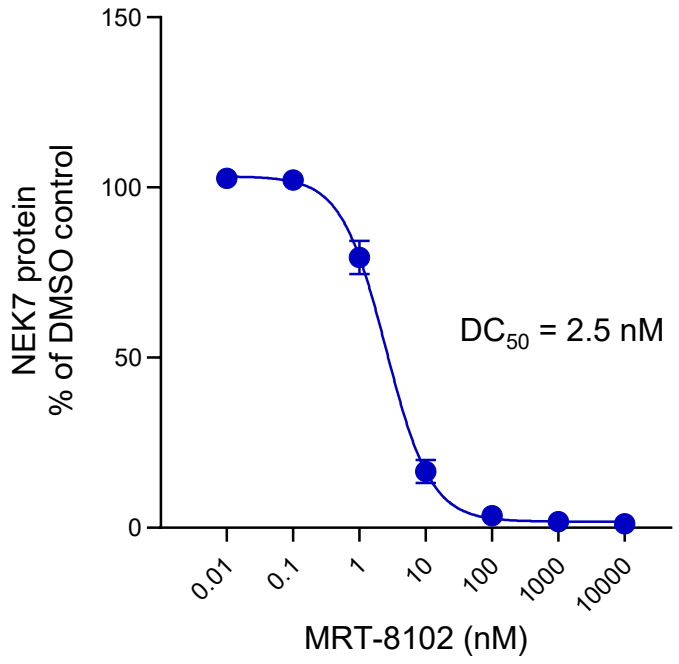


Monte Rosa's rationally designed MGDs have potential applications in Oncology, Immunology, Neuroscience and other therapeutic areas

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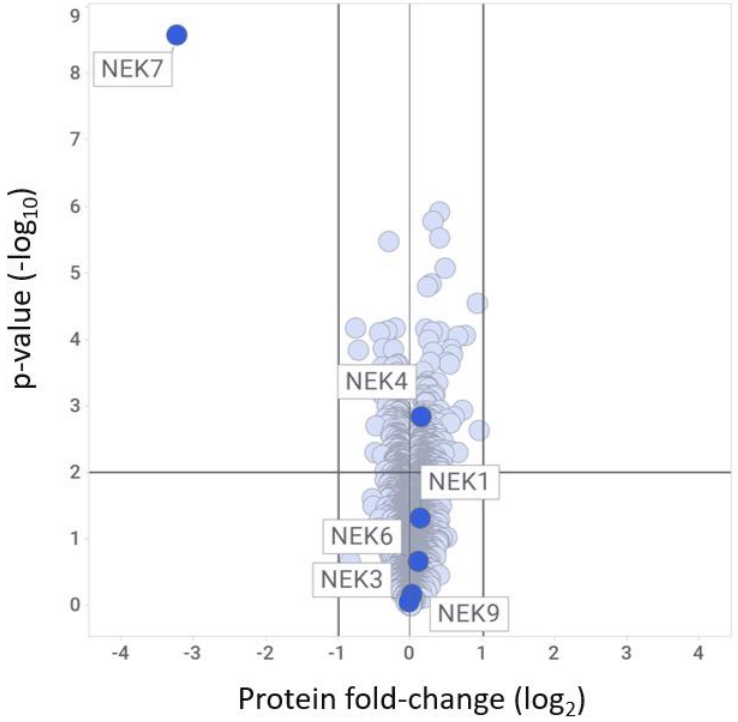
MRT-8102 is a Potent and Selective Molecular Glue Degrader of NEK7

Potent NEK7 degradation



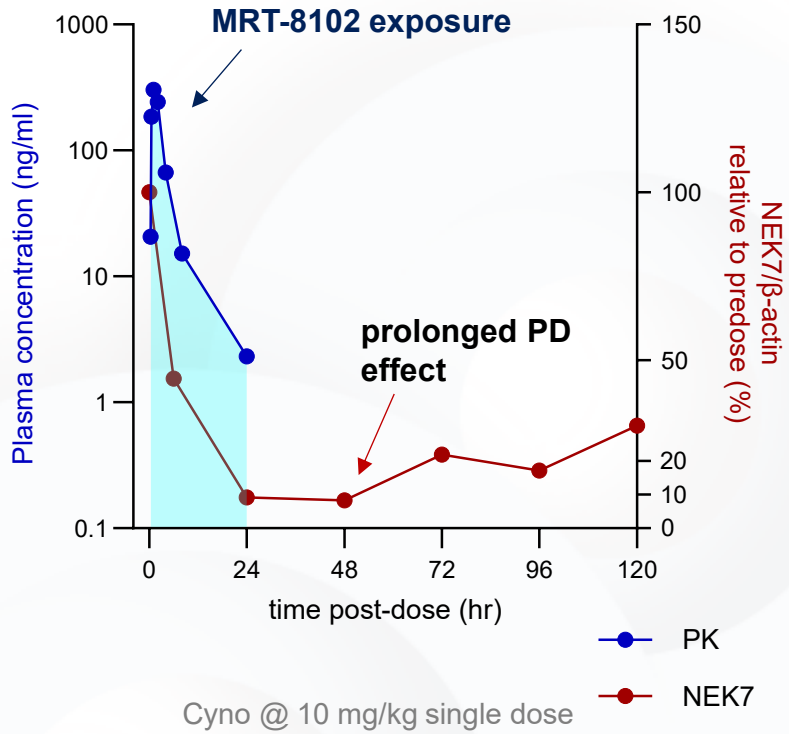
Human PBMC @ 24h treatment

Highly selective by proteomics



No degradation of other known CRBN neosubstrates

Prolonged PD effect relative to exposure



Cyno @ 10 mg/kg single dose

MRT-8102 anticipated to avoid on-off pharmacodynamics and off-target toxicities of NLRP3 inhibitors

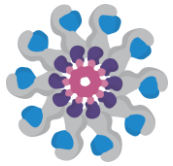
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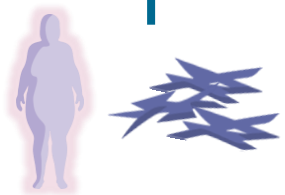
MRT-8102 Inhibits NLRP3 Activity From Pathologic Crystals

Gout is driven by monosodium urate (MSU) crystals

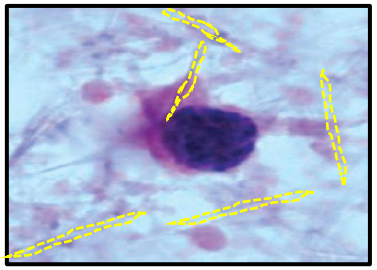


NLRP3/NEK7 inflammasome activation

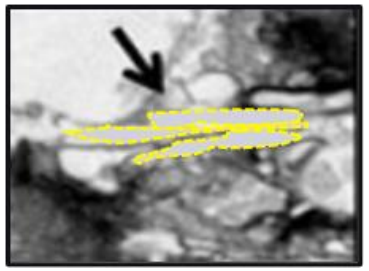




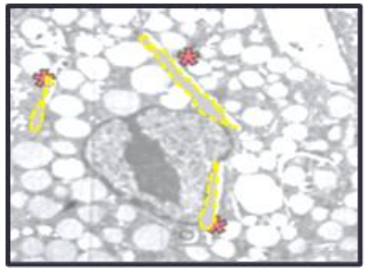
ASCVD and obesity related diseases are driven by cholesterol crystals



Gouty joint synovial fluid contains MSU crystals (yellow) phagocytosed by macrophage

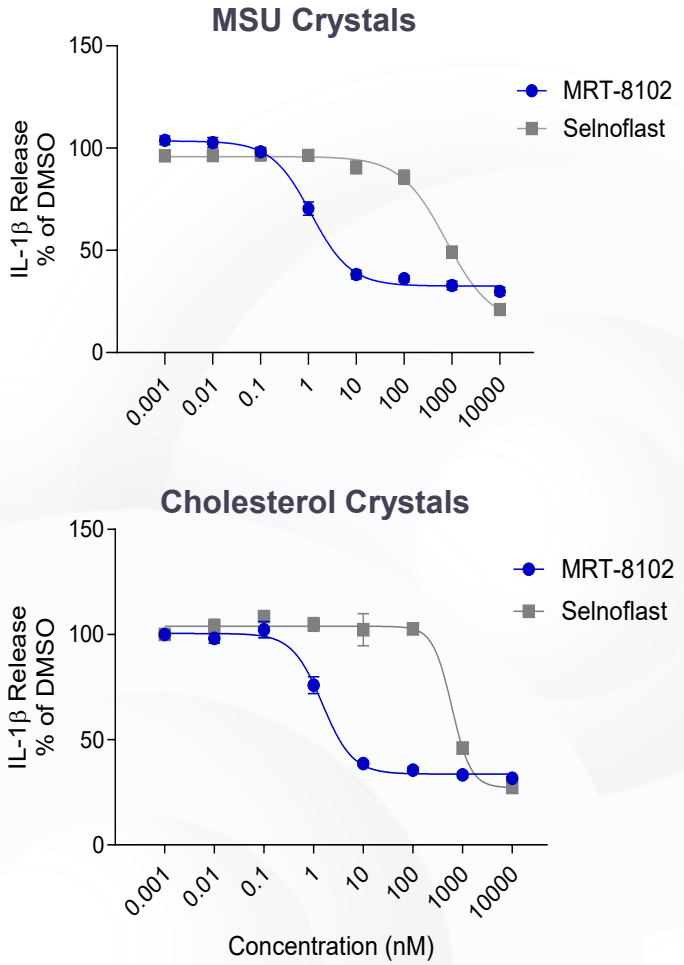


MASH liver lesions contain cholesterol crystals (yellow) within resident cells



Atherosclerotic lesions contain cholesterol crystals (yellow) within foam cell macrophages

MRT-8102 inhibited crystal-mediated IL-1β release



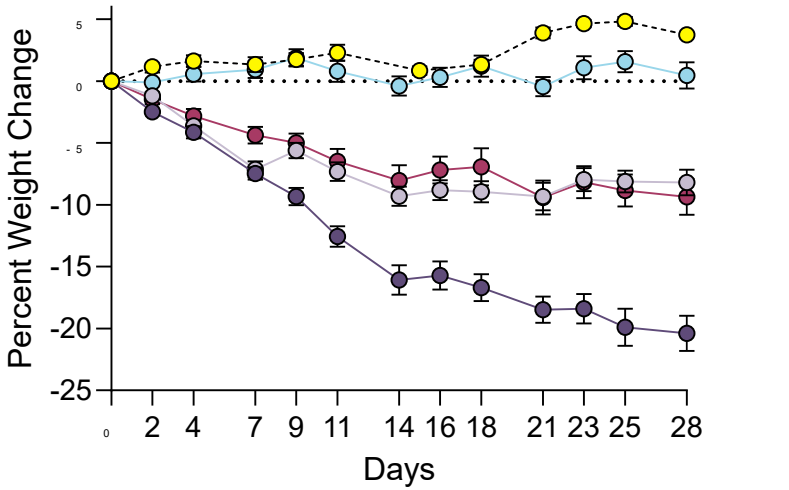
Adapted from Kim et al., 2009 Korean J Pathol; Baumer et al., 2024 Nat Rev Cardiol; Hendrikx et al., 2013 Plos One

Human monocyte-derived macrophages (hMDM) were pre-treated for 24h with varying concentrations of MRT-8102 or selnoflast and then stimulated with LPS (1ug/mL) + MSU crystals (0.2mg/mL) or LPS + cholesterol crystals (1mg/mL) for 6h.

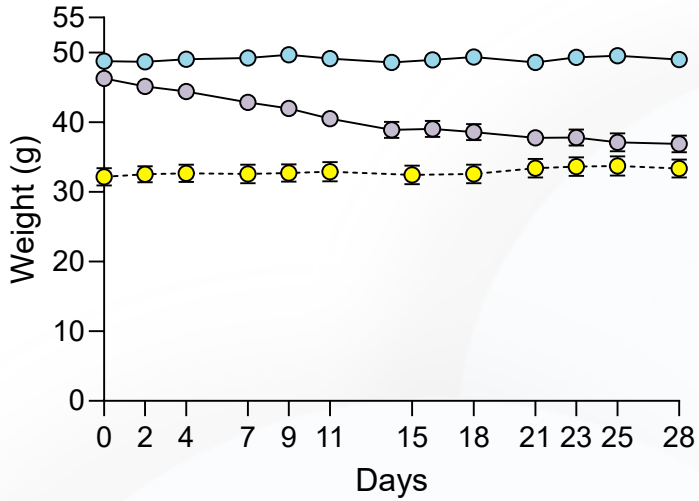
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Therapeutic Effects of MRT-51126, a NEK7 MGD, Tested in Mouse Diet-Induced Obesity Model

MRT-51126 promoted body weight loss alone and with semaglutide



Normalization of absolute body weight by MRT-51126



MRT-51126: 30 mg/kg, BID, p.o. (TID for first 2 days)
Semaglutide (sema): 10 µg/kg, QD, s.c.
CRBN I391V male mice; four months on high-fat diet (HFD) prior to dosing.
Mixed-effects model, tested versus Vehicle unless specified by bracket *** P ≤ 0.001; ****P ≤ 0.0001.

Therapeutic Effects of Surrogate NEK7 MGD, MRT-51126, Tested in Obesity in Cynomolgus Monkeys

HFD cyno colony

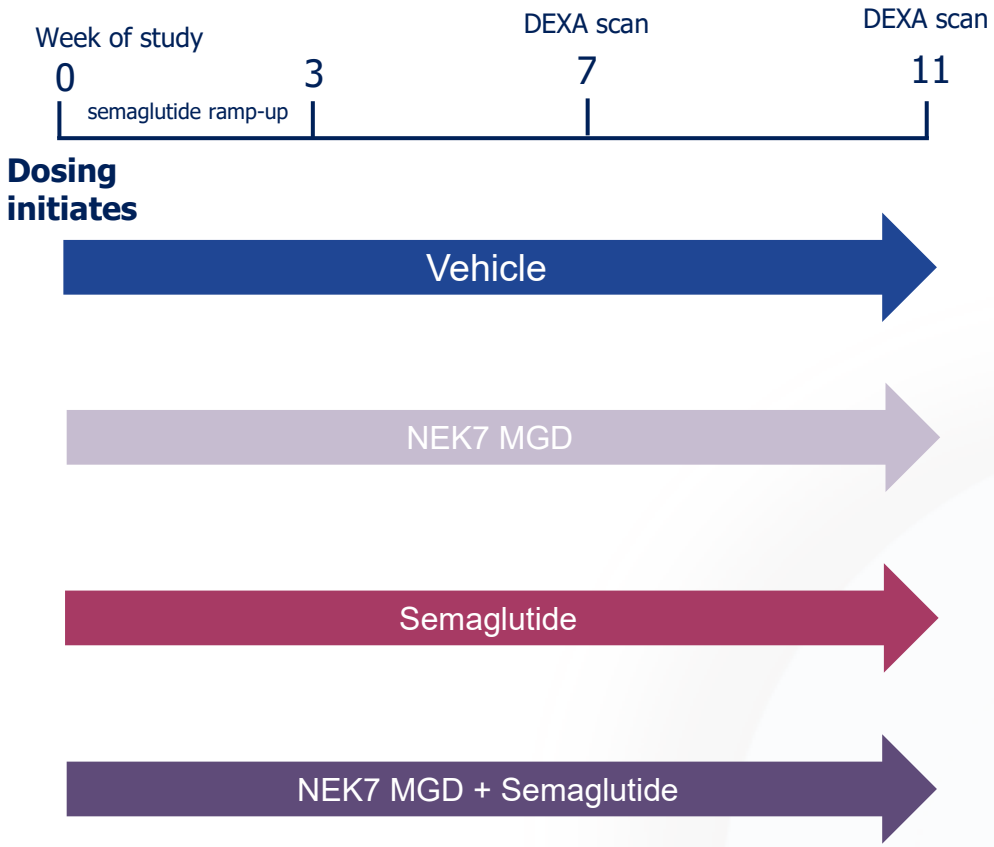
Obese monkeys
(BMI≥40 kg/m^2)

High-fat diet (HFD) fed

Kunming Biomedical Proprietary diet formulated to closely replicate Western diet

Prior to dosing:
Selection from HFD colony, training & randomization

Treatments, doses and schedules



Endpoint evaluations



Body weight change, BMI
Food and water intake
DEXA scans
Behavioral changes
Overt clinical signs



NEK7 degradation
Cytokines



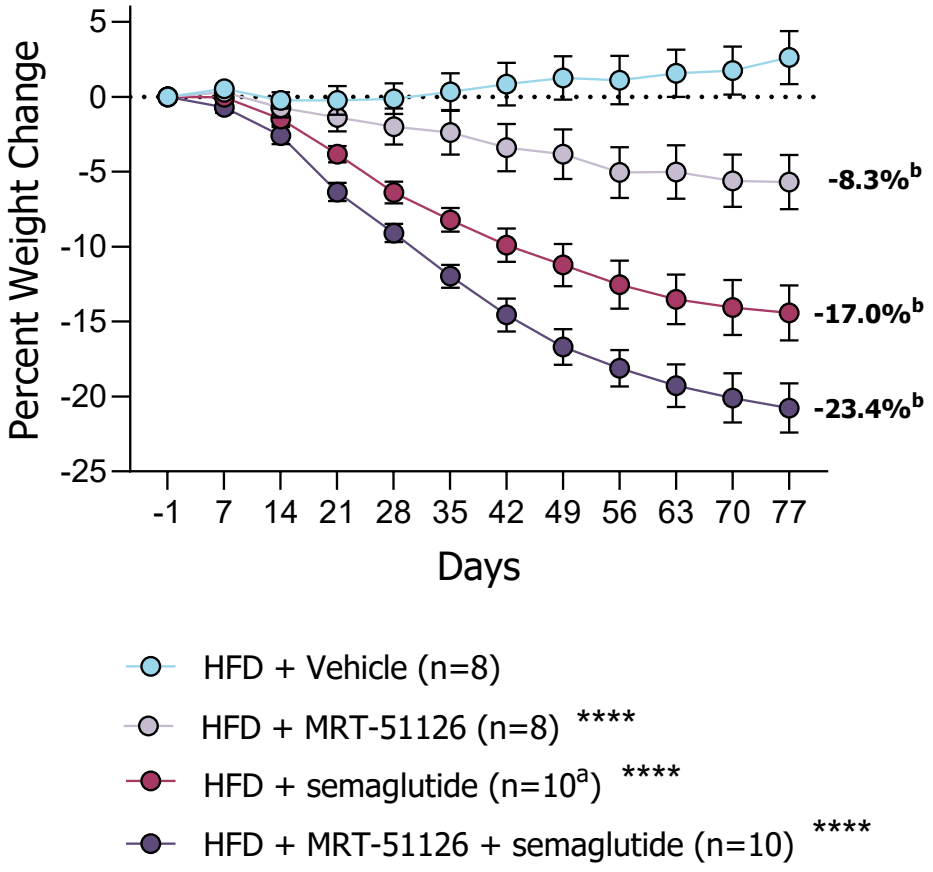
Adipose vs lean mass weight

MRT-51126 dosing: 10 mg/kg QD p.o.
Semaglutide dosing: ramp-up to 30 µg/kg QD s.c.

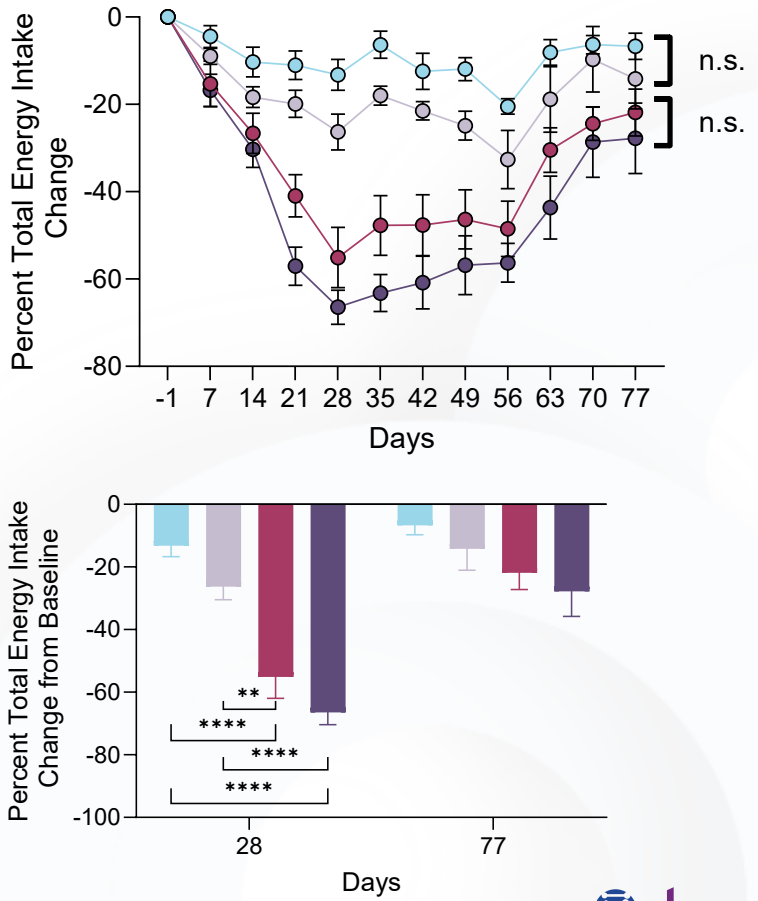
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MRT-51126, Alone or in Combination with Semaglutide, Drove Weight Loss in Cyno Obesity Model

MRT-51126 promoted body weight loss alone and with semaglutide



Mechanisms beyond food intake may have contributed to weight loss

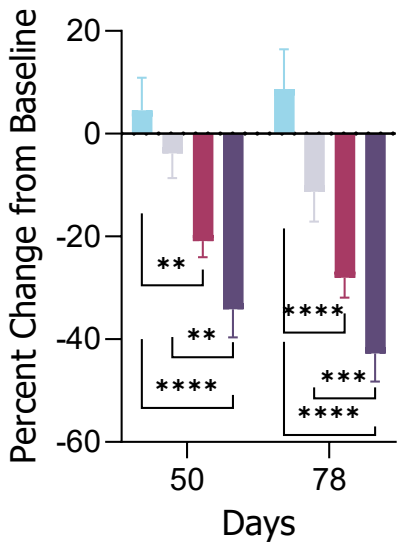


Study subjects selected from colony of HFD (high fat diet)-fed animals and randomized before enrollment; [a]n=9 from Day 56 onwards; [b]Body weight decrease relative to vehicle. [c]DEXA (dual-energy X-ray absorptiometry) body composition analysis performed under anesthesia. 2-Way ANOVA with Šídák's multiple comparisons test. *P ≤ 0.05; **P ≤ 0.01; *** P ≤ 0.001; ****P ≤ 0.0001.

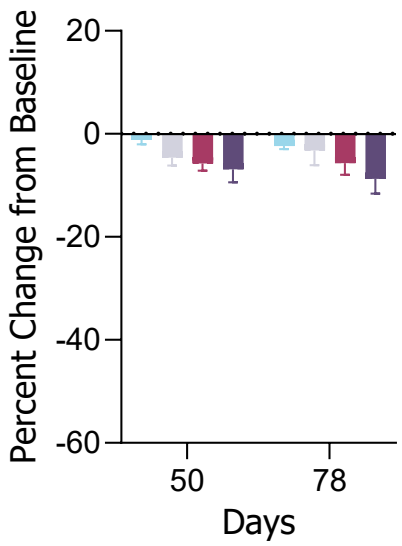
MRT-51126, Alone or in Combination with Semaglutide, Drove Preferential Abdominal Fat Loss in Cyno Obesity Model

Preferential decrease of fat mass over lean mass[c]

Fat mass

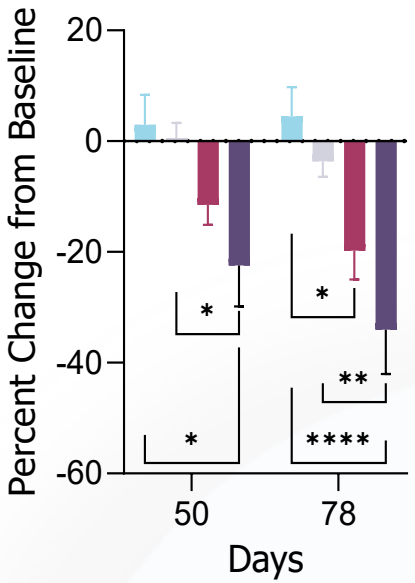


Lean mass

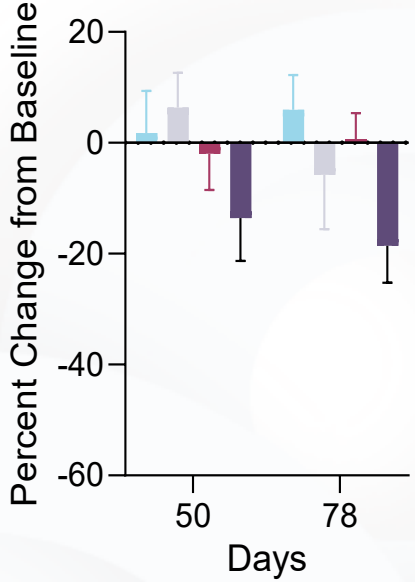


Percent fat (relative to whole body)[c]

Central abdominal fat



Gynoid region fat

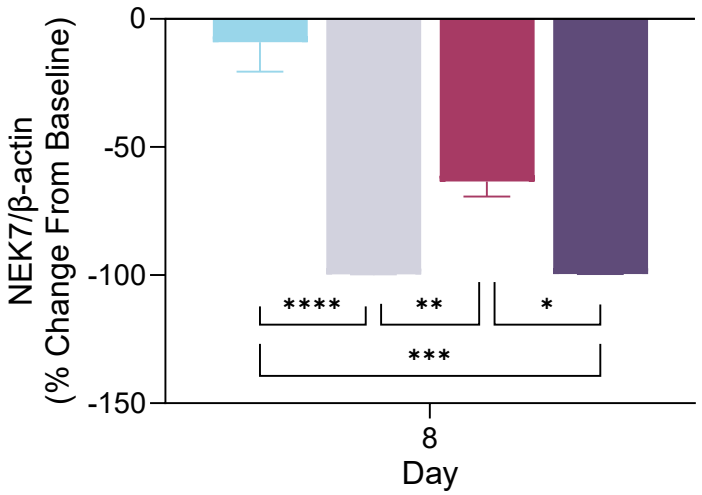


- HFD + Vehicle (n=8)
- HFD + MRT-51126 (n=8)
- HFD + semaglutide (n=10[a])
- HFD + MRT-51126 + semaglutide (n=10)

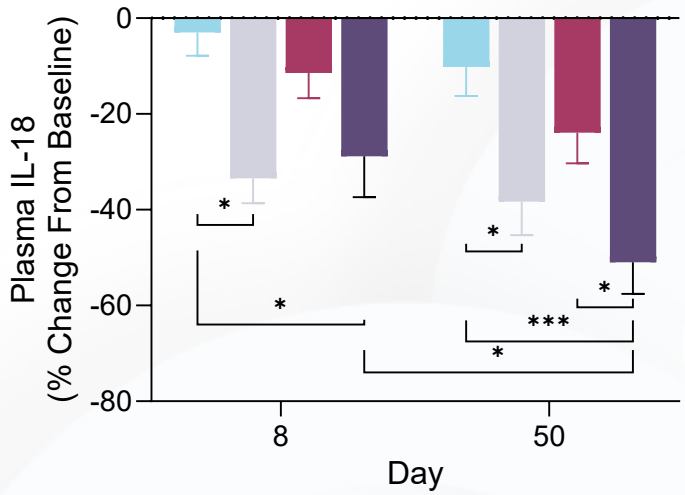
Study subjects selected from colony of HFD (high fat diet)-fed animals and randomized before enrollment; [a]n=9 from Day 56 onwards; [b]Body weight decrease relative to vehicle. [c]DEXA (dual-energy X-ray absorptiometry) body composition analysis performed under anesthesia. 2-Way ANOVA with Šídák's multiple comparisons test. *P ≤ 0.05; **P ≤ 0.01; *** P ≤ 0.001; ****P ≤ 0.0001.

Anti-Inflammatory Activity of MRT-51126 and Semaglutide Partially Overlaps

MRT-51126 induced complete NEK7 degradation in PBMCs; modest reduction for semaglutide



NEK7 degradation/suppression correlated with reduction in endogenous plasma IL-18

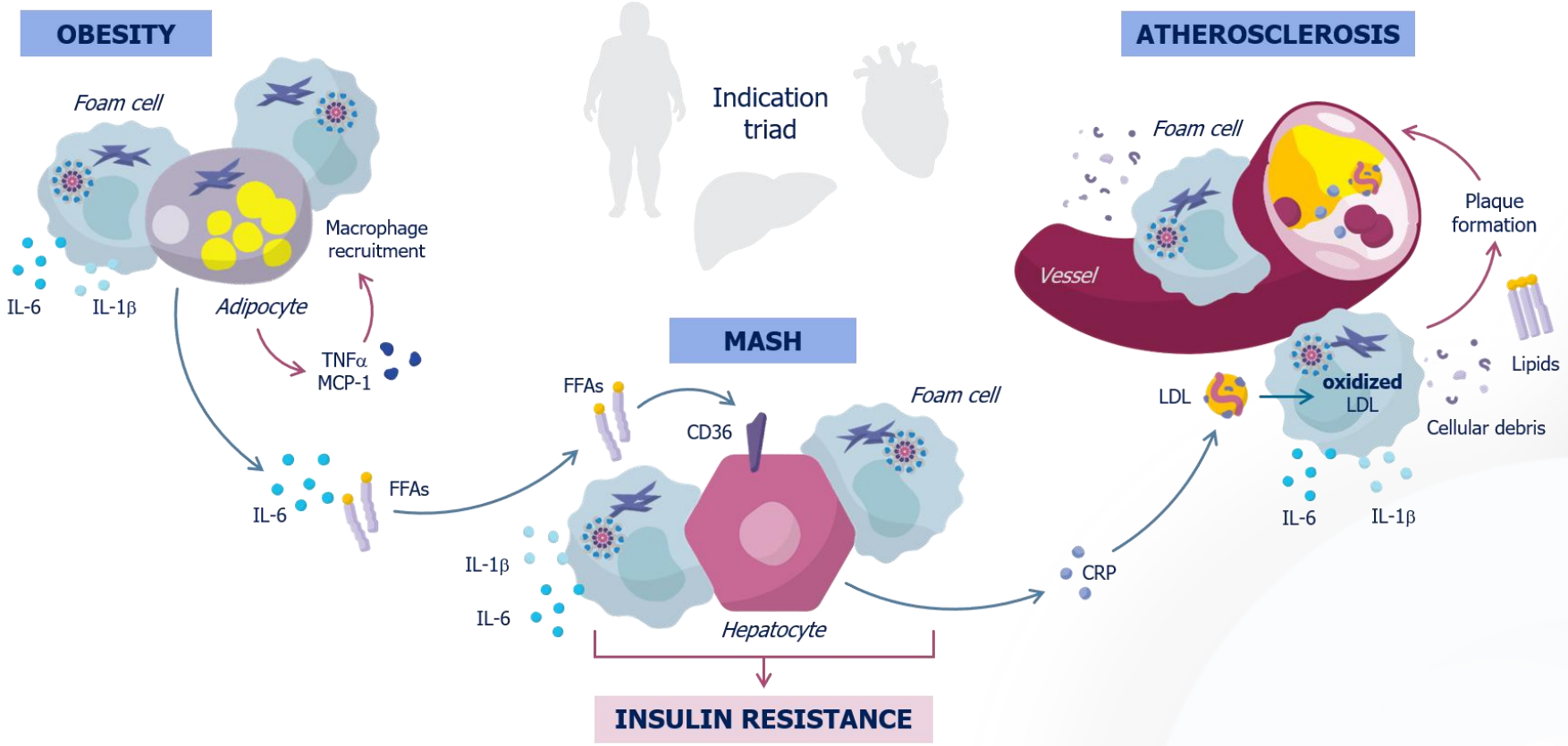


HFD + Vehicle (n=8) | HFD + NEK7 MGD (n=8) | HFD + Semaglutide (n=10) | HFD + NEK7 MGD + Semaglutide (n=10)

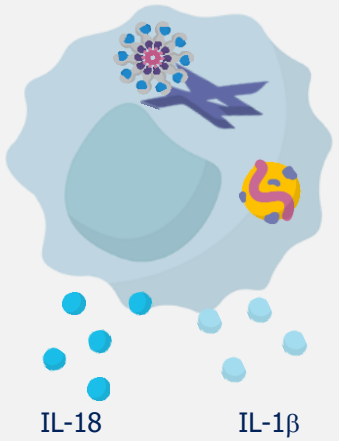
Semaglutide mechanism of action impacts NLRP3/NEK7 pathway activity, further supporting potential combination strategy with NEK7 MGD

2-Way ANOVA with Šídák's multiple comparisons test. *P ≤ 0.05; **P ≤ 0.01; *** P ≤ 0.001; ****P ≤ 0.0001.

Obesity, MASH and ASCVD are Metabolic Diseases Connected by Pathological Activation of NLRP3 in Tissue-Resident Myeloid Cells



NLRP3/NEK7 inflammasome activation drives multiple pathologies



NEK7 MGD

- NLRP3 activation drives pathologic inflammation across metabolic diseases
- NEK7 MGD can reduce local/systemic inflammation to reduce severity of disease
- GLP-1R agonism, in combination with NEK7 degradation could improve clinical outcomes

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Acknowledgements



Boston



Basel

Monte Rosa Therapeutics: Philippe Pagni, Arvin Iracheta-Vellve, Daric Wible, Sophia Nguyen, Maciej Cabanski, Vanessa Verdine, Hoson Chao, Keerthana Gosala, Devin Jenness, Megan Sheehan, Bronwyn Owens, Caiyue Xu, Mason Yeh, Ela Hirsch, Joy Wei, Karin von Hodenberg, Lisa Cantagallo, Luca Moccia, Renpeng Liu, Terry White, Tess Smalbach, Christina Ricciardelli, Laura Roditi, Sara Castillo, Anna Kostikova, Markus Baumann, Kris Meier, Laura McAllister, Elisa Liardo, John Castle, Sharon Townson, Chris King, Magnus Walter, Ari Pano, Filip Janku, Markus Warmuth, Manav Korpal

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Q A