MRT-6160, a highly selective and first-in-class VAV1-directed molecular glue degrader, demonstrates activity in multiple immune-mediated disease models

Dr. Adam N.R. Cartwright | 21 January 2026 | Keystone

Monte Rosa Therapeutics

Disclosures

I have the following relevant financial relationships to disclose:

- Employee for Monte Rosa Therapeutics
- Stock options for Monte Rosa Therapeutics (GLUE)

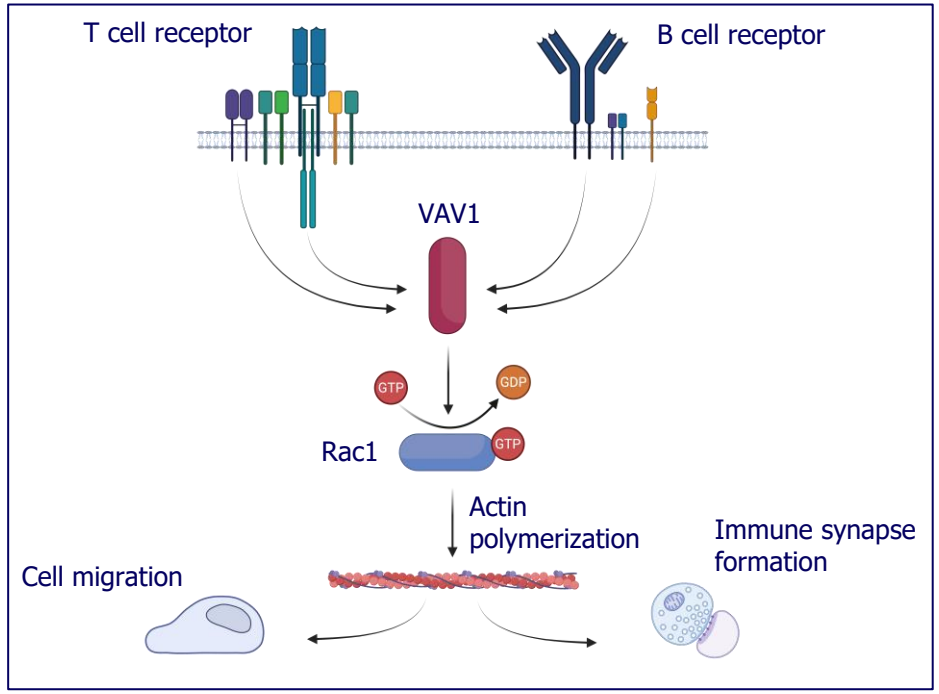
Monte Rosa Therapeutics has a global exclusive license agreement with Novartis to advance VAV1 MGDs including MRT-6160

Summary: MRT-6160, a VAV1-Targeting MGD for the Treatment of Multiple Immune-Mediated Diseases

- MRT-6160 is a **highly selective, first-in-class molecular glue degrader of VAV1**, a key T/B cell signaling protein
- In preclinical studies, oral administration of **MRT-6160 attenuates disease progression** across a range of *in vivo* immune-mediated disease models **involving T and B cells**
- In a healthy volunteer clinical trial [NCT06597799], MRT-6160 demonstrated deep VAV1 degradation of greater than 90%, **significant T and B cell functional inhibition**, as well as significant inhibition of cytokines commonly associated with multiple immune-mediated diseases
- These data highlight the **key role and translatability of VAV1 in T/B cell** function in preclinical studies to the clinical setting
- These findings reinforce the broad therapeutic potential of MRT-6160 across **multiple immune-mediated diseases including SLE, Sjögren's disease, rheumatoid arthritis, IBD and others**

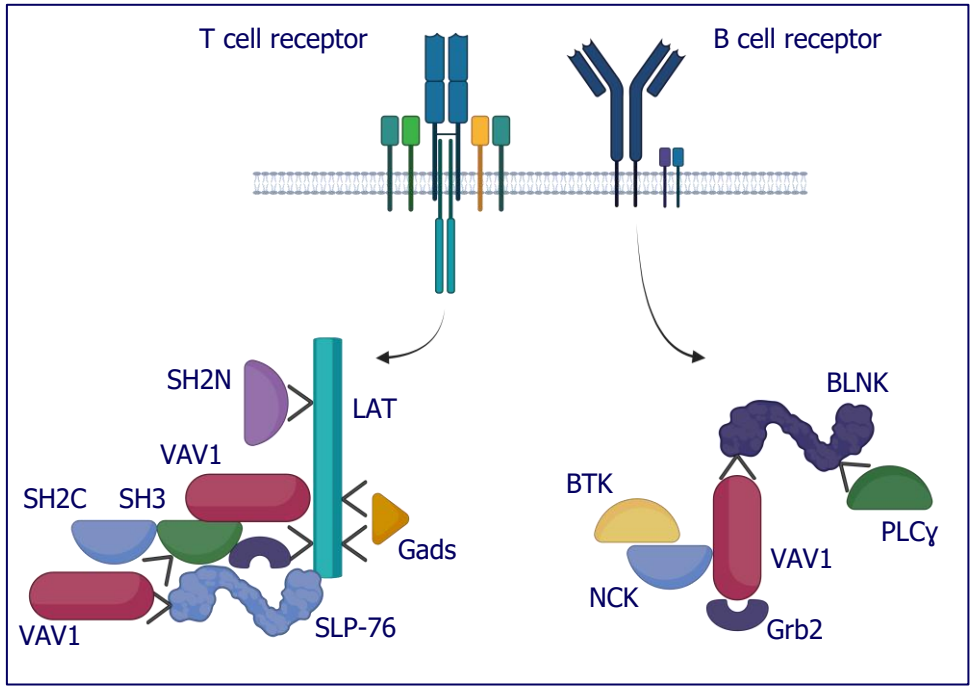
VAV1 Possesses GEF-Dependent and –Independent Functions

GEF-dependent enzymatic functions



- Phosphorylation of VAV1 activates guanine nucleotide exchange functions (GEF)
- VAV1 GEF activity activates Rho family GTPases such as Rac1 and Cdc42
- Rac1 and Cdc42 control actin skeleton rearrangement, essential for immune synapse formation and cell motility

GEF-independent scaffolding function



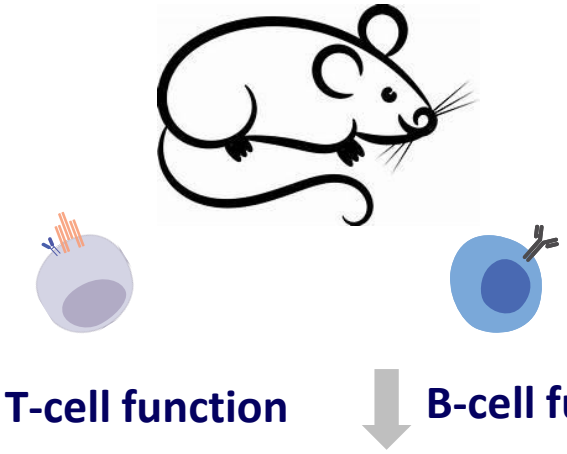
- VAV1 functions as a scaffolding protein by organizing signaling complexes
- VAV1 binds to key TCR/BCR signaling proteins, such as SLP-76 and PLCγ, to form signaling microclusters
- Formation of scaffolded microclusters facilitate complete and efficient activation of immune cells

Adapted from Neurath and Berg. Trends Immunol. (2024)

VAV1 is a Highly Validated Target for Attenuating T- and B-cell Activity

VAV1$^{-/-}$ mice are viable, fertile, and display loss-of-function T- and B-cell phenotypes

***VAV1*$^{-/-}$ mice**



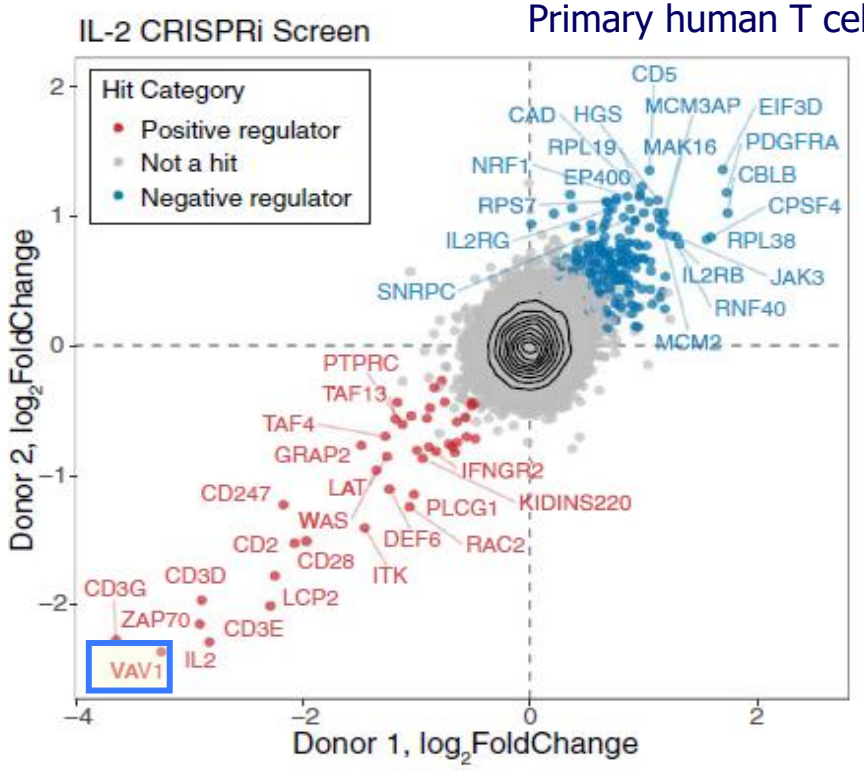
T-cell function **B-cell function**

- Impaired T-cell proliferation and cytokine production
- Impaired B-cell proliferation and immunoglobulin production
- Evidence of impaired T-cell dependent B-cell response

Betzler et al., Front Cell & Dev Bio 2022
Turner et al., Nat Rev Immun 2002
Bachman et al., J. Immun 1999
Fischer et al., Curr Biol 1998

Multiple CRISPR screens identified VAV1 as key player in primary human T-cell function

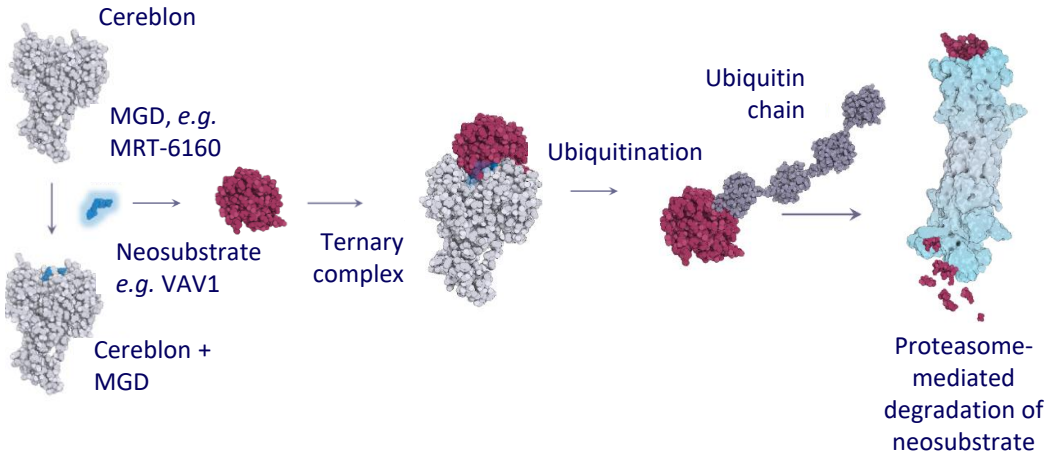
Primary human T cells



Schmidt et al., Science 2022

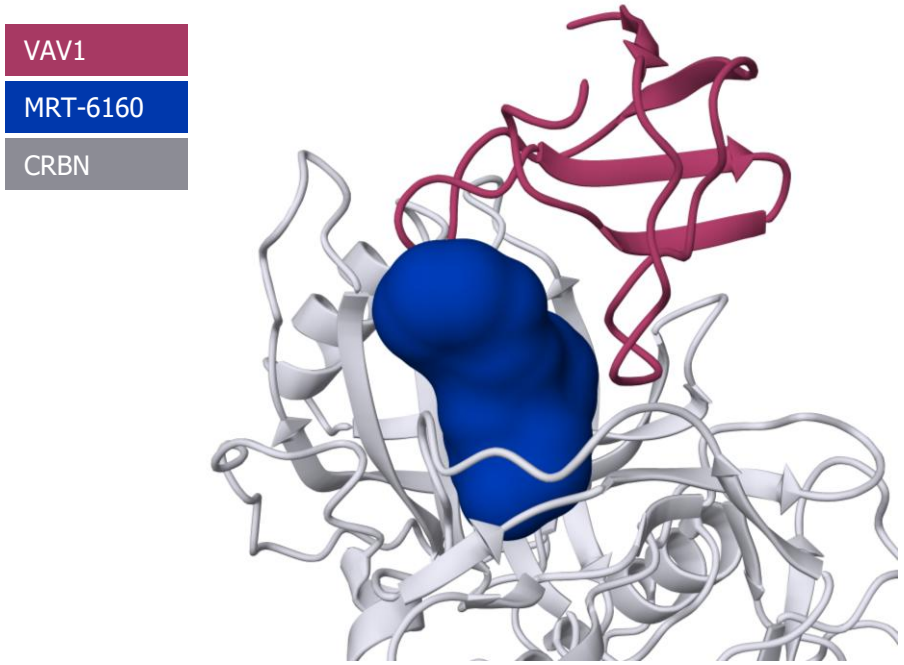
MRT-6160, A Molecular Glue Degrader Drugging the Undruggable

Molecular glues reprogram E3 ubiquitin ligases to induce degradation of target 'neosubstrate' proteins



MGD-induced ternary complex formation with cereblon and target protein (e.g. VAV1)

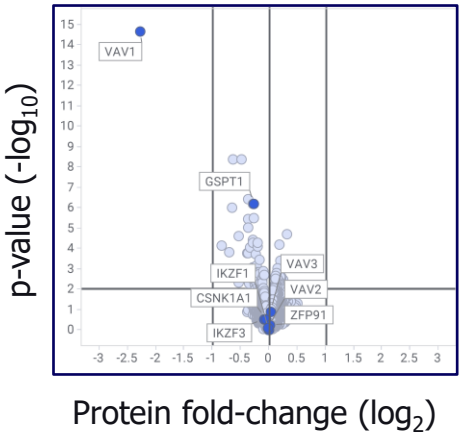
MRT-6160 enables the targeting of VAV1 for proteasomal degradation

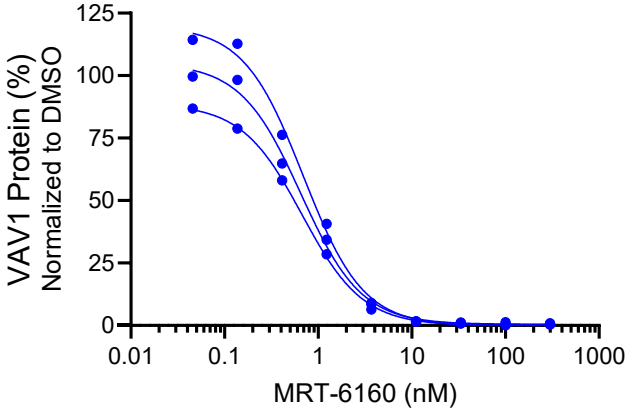


Cryo-EM structure of MRT-6160 in ternary complex with CRBN and VAV1

MRT-6160 Demonstrates Exquisite Potency and Selectivity for VAV1 In Human and Mouse

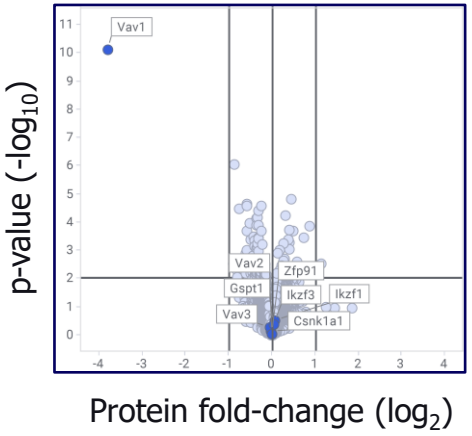
MRT-6160 demonstrates high selectivity and potency for human VAV1 in PBMCs

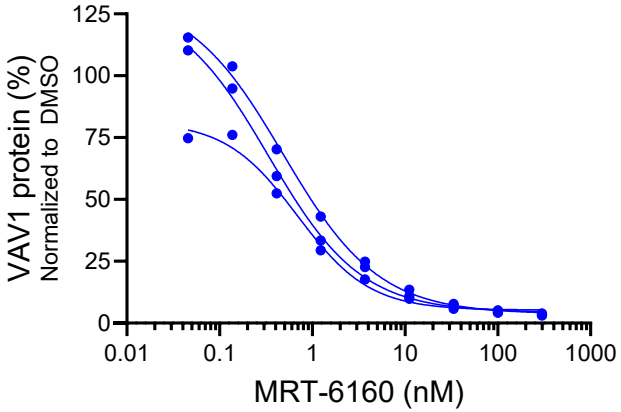




Human PBMCs were treated with 10 μM (proteomics) or increasing concentrations of (JESS) MRT-6160 for 24 hours then assessed by quantitative tandem mass tag proteomics (left) or JESS (normalized to β-actin)

MRT-6160 demonstrates high selectivity and potency for mouse Vav1 in splenocytes



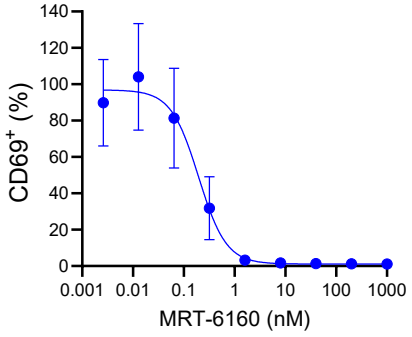


Mouse splenocytes were treated with 10 μM (proteomics) or increasing concentrations of (JESS) MRT-6160 for 24 hours then assessed by quantitative tandem mass tag proteomics (left) or JESS (normalized to β-actin)

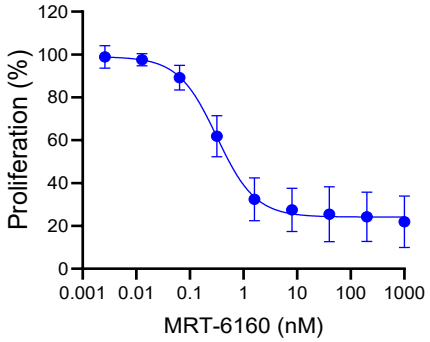
MRT-6160 Reduces TCR- and BCR-Mediated Effector Functions *In Vitro*

MRT-6160 inhibits TCR-mediated T-cell activation, proliferation, and pro-inflammatory cytokine production

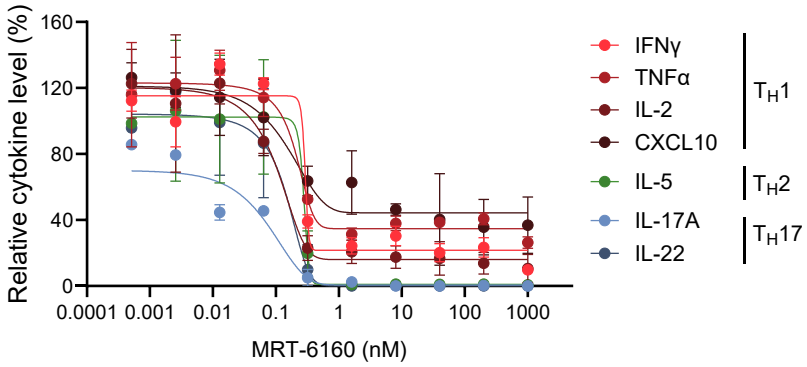
CD69



Proliferation



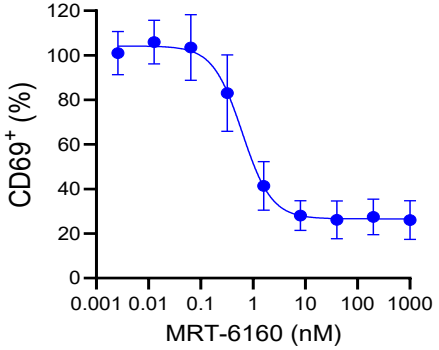
Cytokines



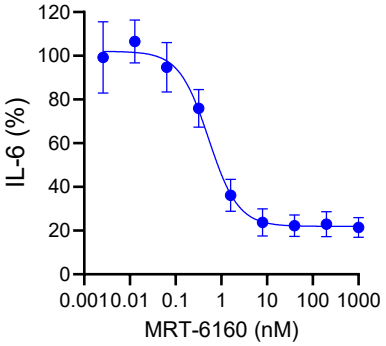
Purified primary human pan-T cells pre-treated with MRT-6160 for 24 hrs followed by TCR stimulation with αCD3/αCD28 and analyses by flow cytometry (CD69, proliferation) or MSD (cytokines).

MRT-6160 inhibits BCR-mediated B-cell activation, effector functions and differentiation

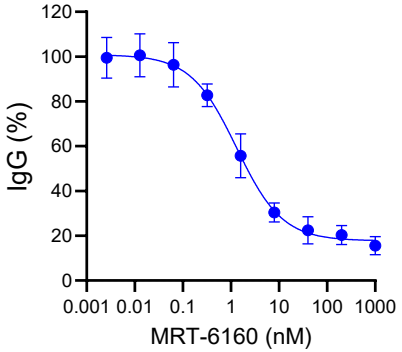
CD69



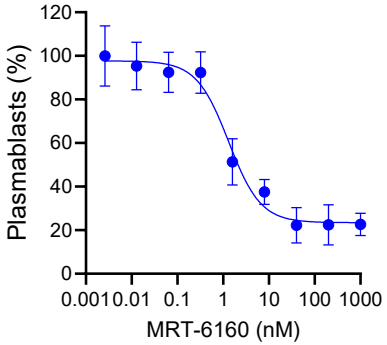
IL-6



Soluble IgG



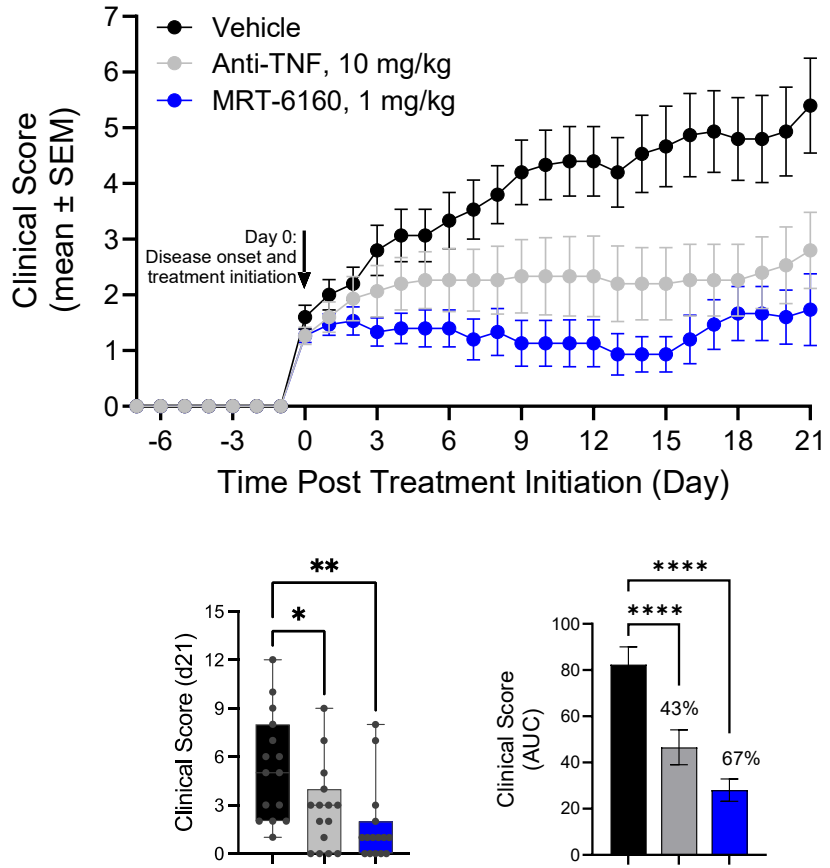
Plasmablast differentiation



Purified primary human B-cells pre-treated with MRT-6160 for 24 hrs followed by stimulation with anti-IgM and IL-4 and analysis of CD69 expression and IL-6 secretion 24 hrs post stimulation or stimulation with anti-IgM, sCD40L, IL-21, IL-2, and BAFF and analysis of soluble IgG and plasmablast differentiation on day 5 post stimulation.

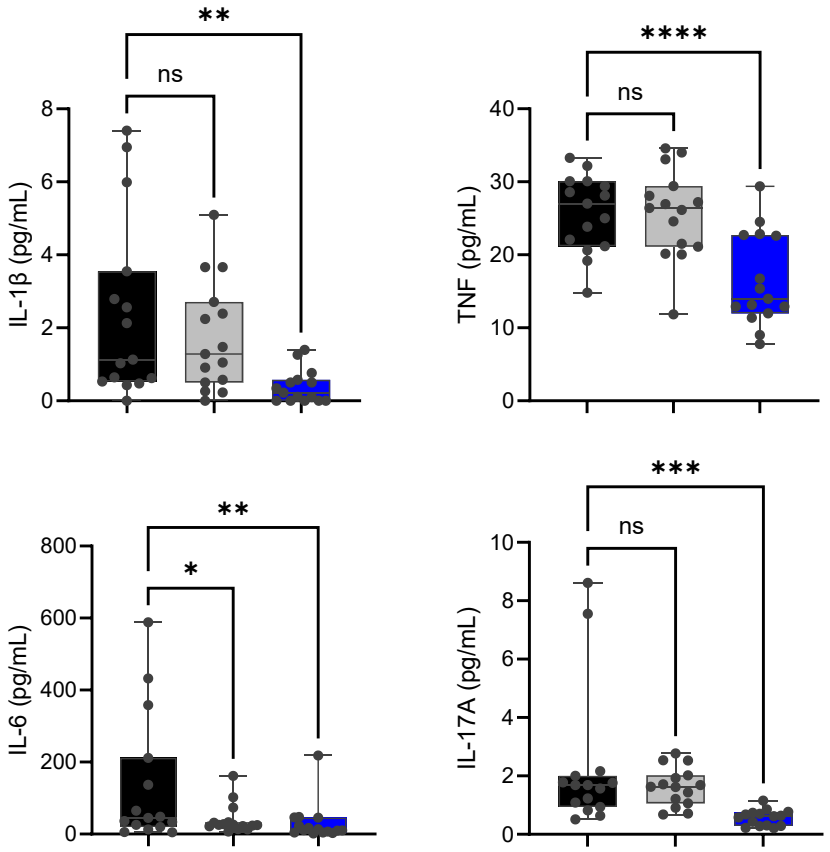
MRT-6160 Inhibits Disease Progression and Pro-inflammatory Cytokine Production in a Collagen-Induced Arthritis Model

MRT-6160 inhibited disease progression and disease severity of a CIA model



DBA/1 mice were immunized twice with bovine collagen-II emulsified in complete Freund's adjuvant 21 days apart then monitored for clinical score. Mice were enrolled in treatments groups following a clinical score 2.

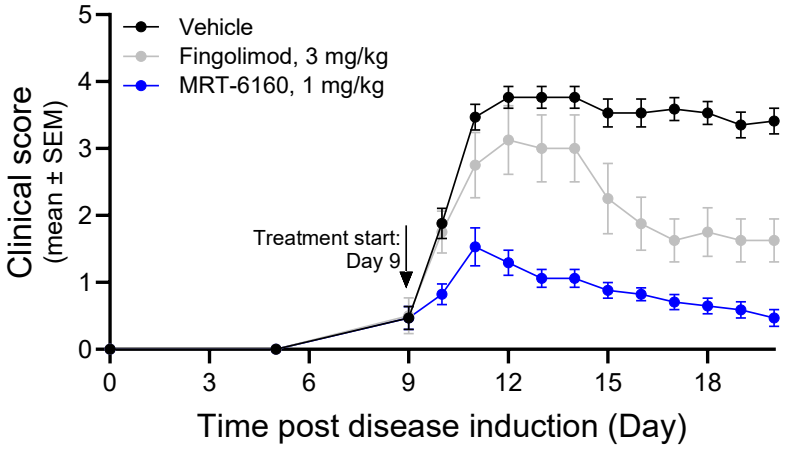
MRT-6160 reduced secretion of key disease-associated serum cytokines

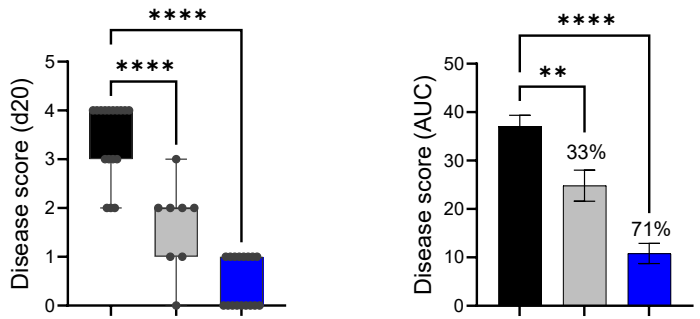


At study termination, serum samples were assessed for cytokine levels by MSD

MRT-6160 Inhibits Disease Progression, Pro-inflammatory Cytokine Production, and Neuroinflammation in an EAE Model

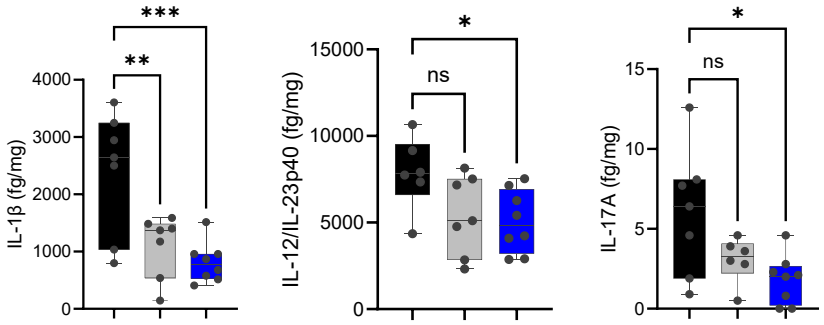
MRT-6160 reversed disease progression resulting in lower overall disease burden than standard of care

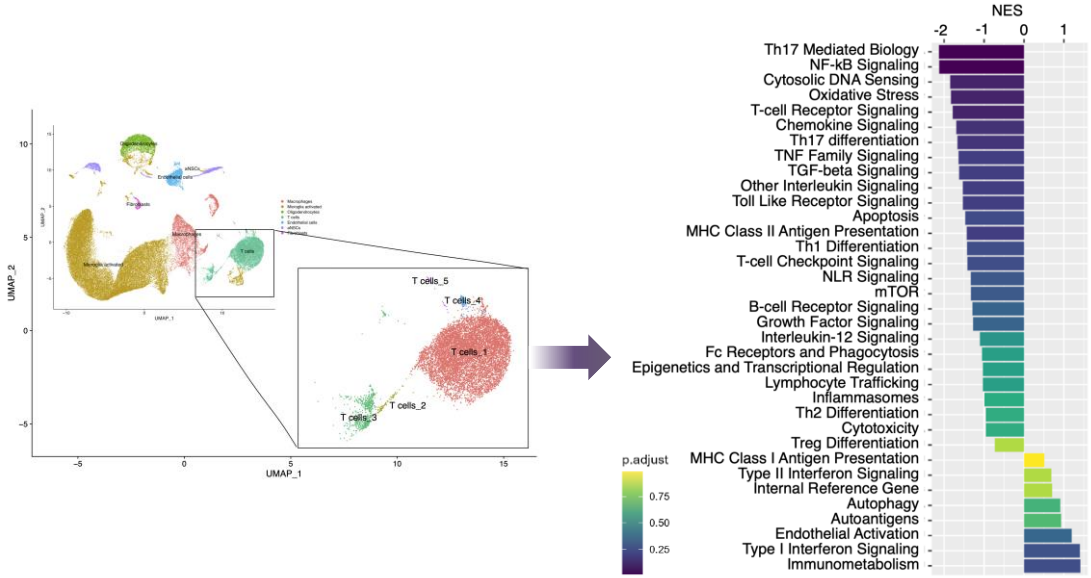




C57BL/6 mice were immunized with human full-length MOG protein emulsified in complete Freund's adjuvant, given pertussis toxin i.p. on the day of immunization and 2 days later, then monitored for clinical score. Mice were treated from onset of disease, here Day 9, post-immunization

MRT-6160 reduced expression of cytokines, tissue damage, and T cell pathway expression in the spinal cord

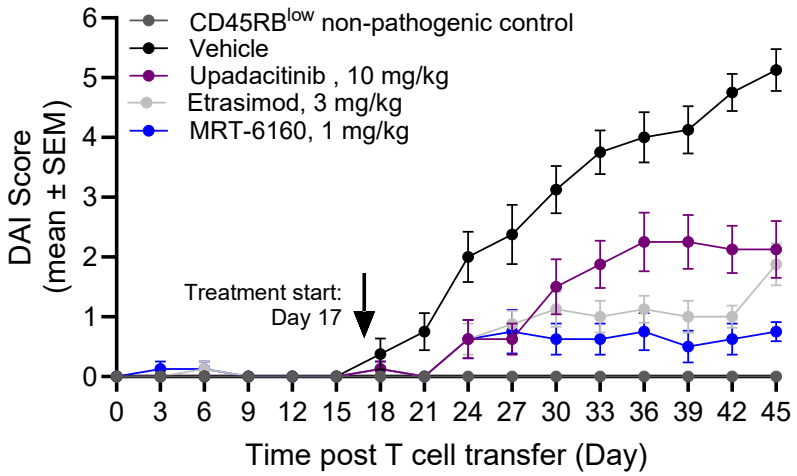


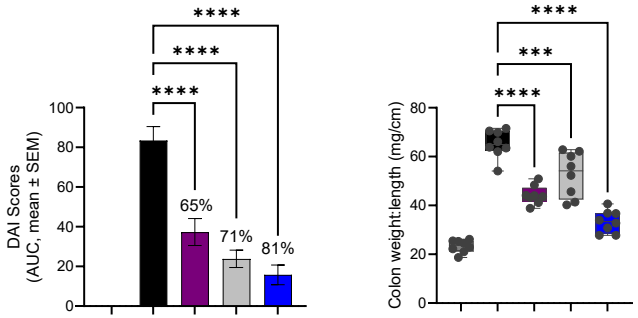


Spinal cords were excised at the study termination and assessed for cytokine levels in tissue homogenate by MSD or for histopathology (immune infiltration, demyelination, and lesion area %) or by single cell RNA-sequencing.

MRT-6160 Inhibits Disease Progression, Pro-inflammatory Cytokine Production, and Colon Damage in a T Cell Transfer Colitis Model

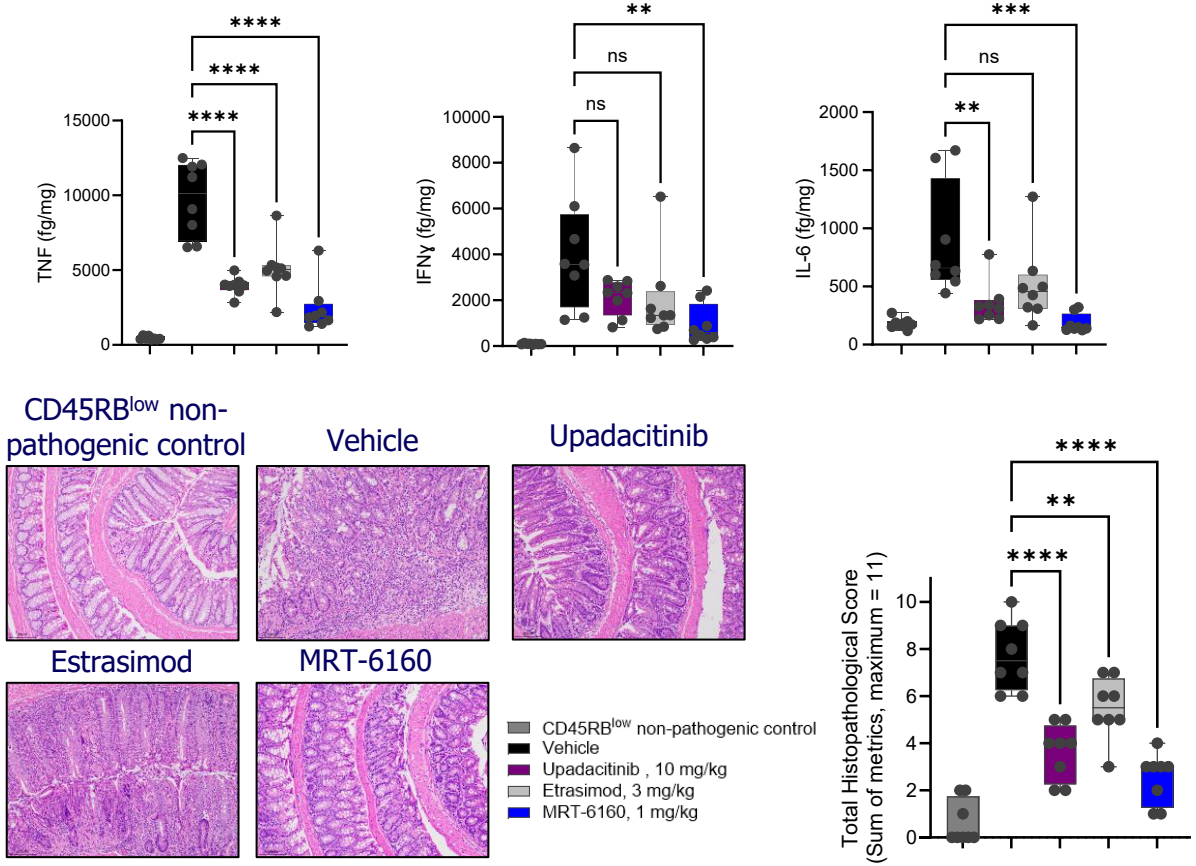
MRT-6160 inhibited disease progression and colon weight:length ratio





Naïve CD45RB^{high} or control CD45RB^{low} cells were transferred from Balb/c mice into CB17 SCID mice then monitored for clinical score. Mice were treated from Day 17 post T cell transfer.

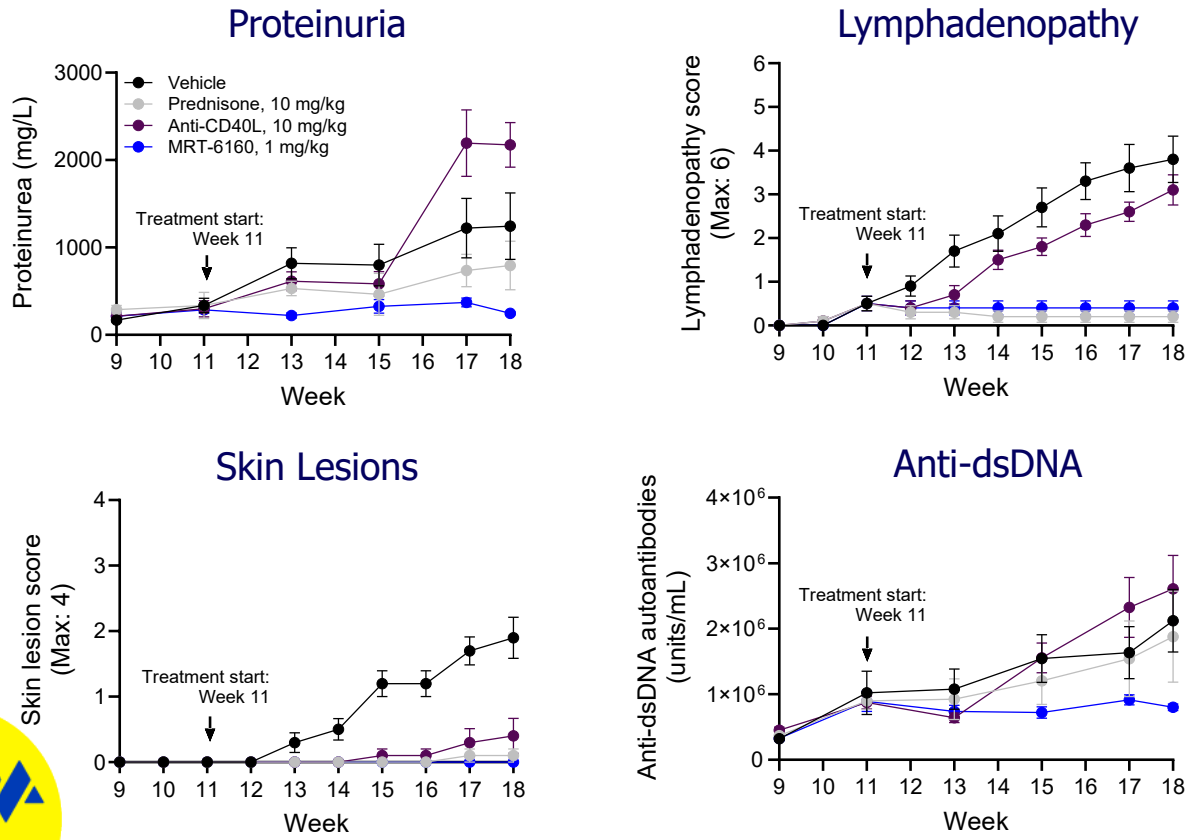
MRT-6160 reduced expression of key disease-associated cytokines and tissue damage in the colon



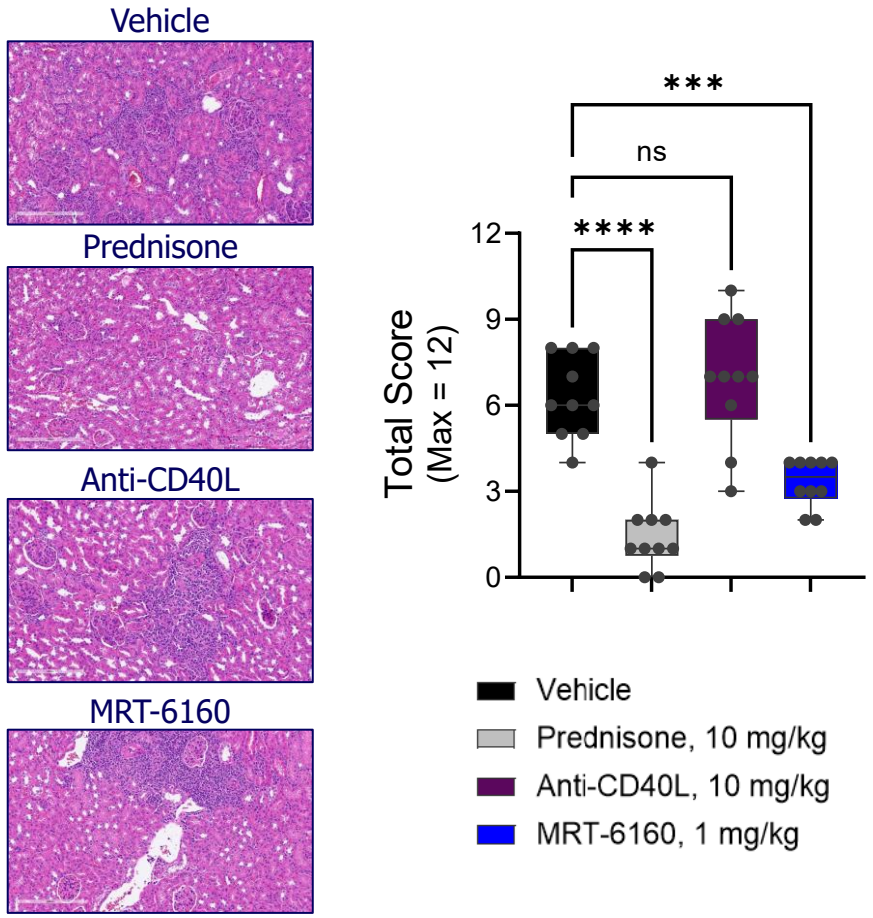
Colons were excised at the study termination and assessed for cytokine levels in tissue homogenate by cytokine bead array or for histopathology (crypt architecture, inflammatory cell infiltration, muscle thickening, goblet cell presence, and crypt abscess presence)

MRT-6160 Inhibits Disease Progression, Autoantibody Production, and Nephritis in the MRL-Fas^{lpr} Lymphoproliferative Autoimmune Model

MRT-6160 inhibits disease progress across multiple metrics in the MRL-Fas^{lpr} autoimmune model



MRT-6160 reduces kidney histopathology including lupus and interstitial nephritis

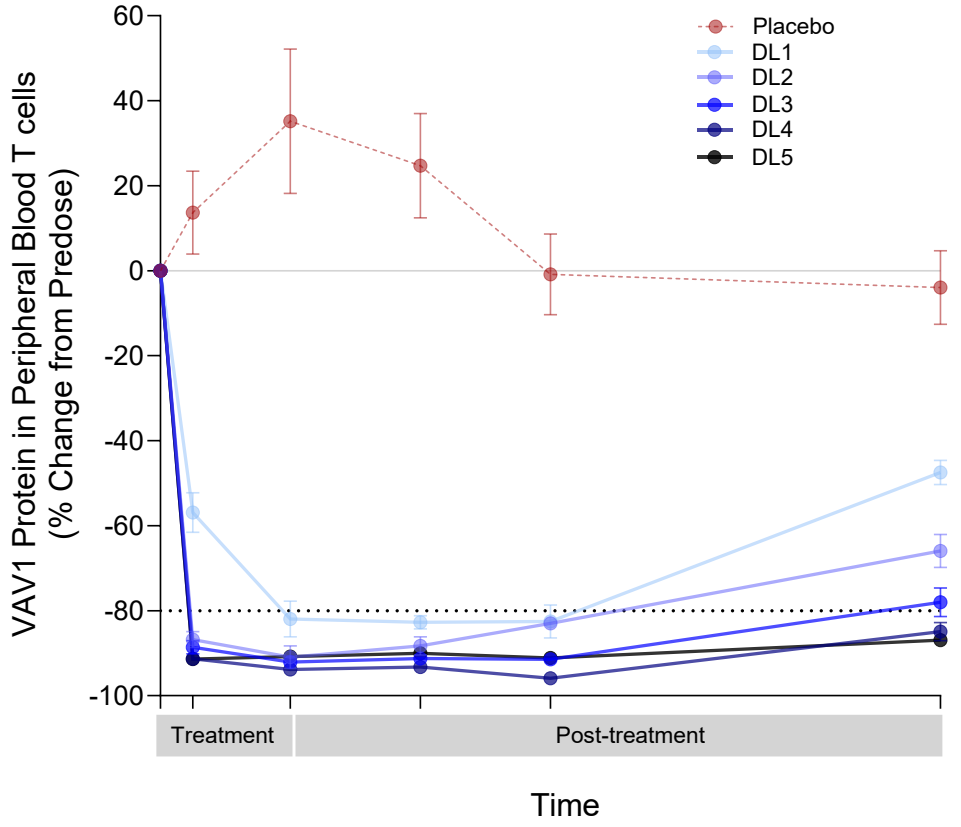


MRL-Fas^{lpr} mice were treated from age of 11 weeks until 18 weeks. Mice were assessed weekly for body weight, lymphadenopathy, and skin lesions and every 2 weeks for proteinuria and serum anti-dsDNA antibody levels.

Kidneys were excised at the study termination and assessed for histopathology (lupus glomerulonephritis, interstitial nephritis, and vasculitis)

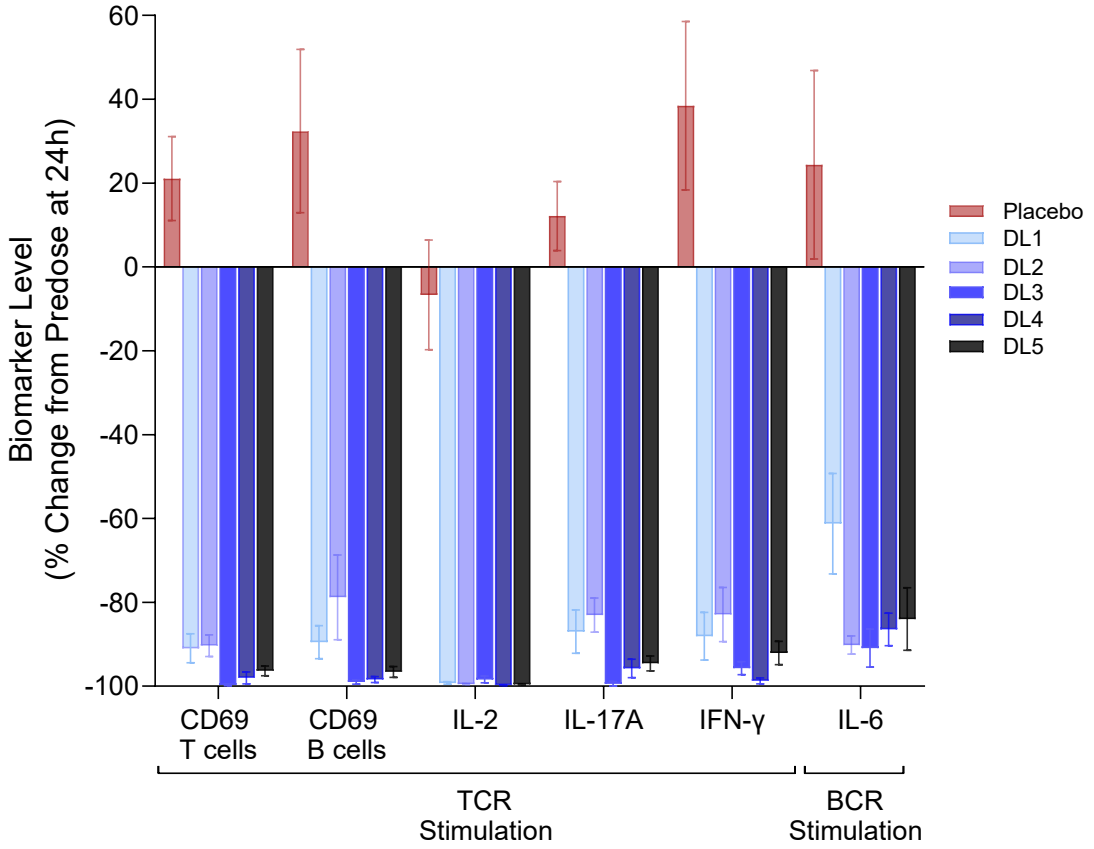
VAV1 Degradation by MRT-6160 Exceeds 90% with Significant Functional Inhibition of T and B Cells following a Single Dose Administration

Dose-dependent degradation of VAV1 in peripheral blood T cells



Healthy volunteers were administered a single oral dose of MRT-6160 at increasing dose levels and VAV1 protein levels in peripheral blood T cells were assessed by flow cytometry at time points indicated and shown relative to pre-dose

Attenuation of immune cell activation (CD69 expression) and cytokine production in T and B cells



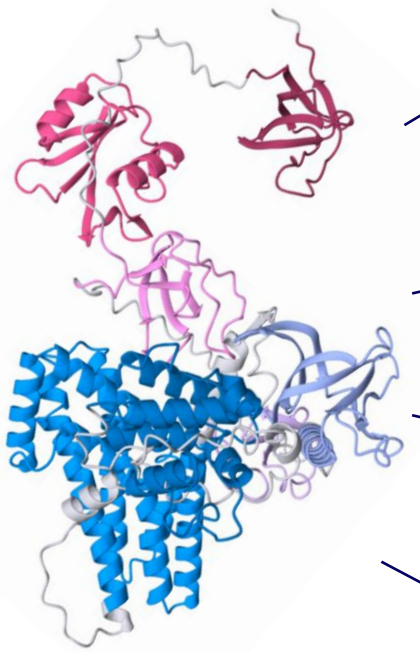
Whole blood was isolated from healthy volunteers after treatment and stimulated as indicated then biomarkers assessed. Data show change in biomarkers relative to pre-stimulation baseline

NCT06597799

VAV1 is an Upstream Targeting Node Associated with Clinically Validated Pathways

VAV1 signaling is associated with several T and B cell immunologic outcomes

Clinically validated pathway in autoimmune/inflammatory disease



VAV1

T cell activation

ORENCIA® (abatacept)

RINVOQ® upadacitinib

B cell activation/Plasma cell differentiation (Antibody production)

Rituxan® Rituximab

VYVGART® Hytrulo

Th17 response

Cosentyx® (secukinumab)

omvoh™ (mirikizumab-mrkz) 300 mg/15 mL infusion | 100 mg/mL injection

Pro-inflammatory cytokine production

HUMIRA® adalimumab

ACTEMRA® tocilizumab


Thank you
Monte Rosa
Therapeutics