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Autoimmune Pathway Blockade By A Potent Orally Bioavailable STING Antagonist

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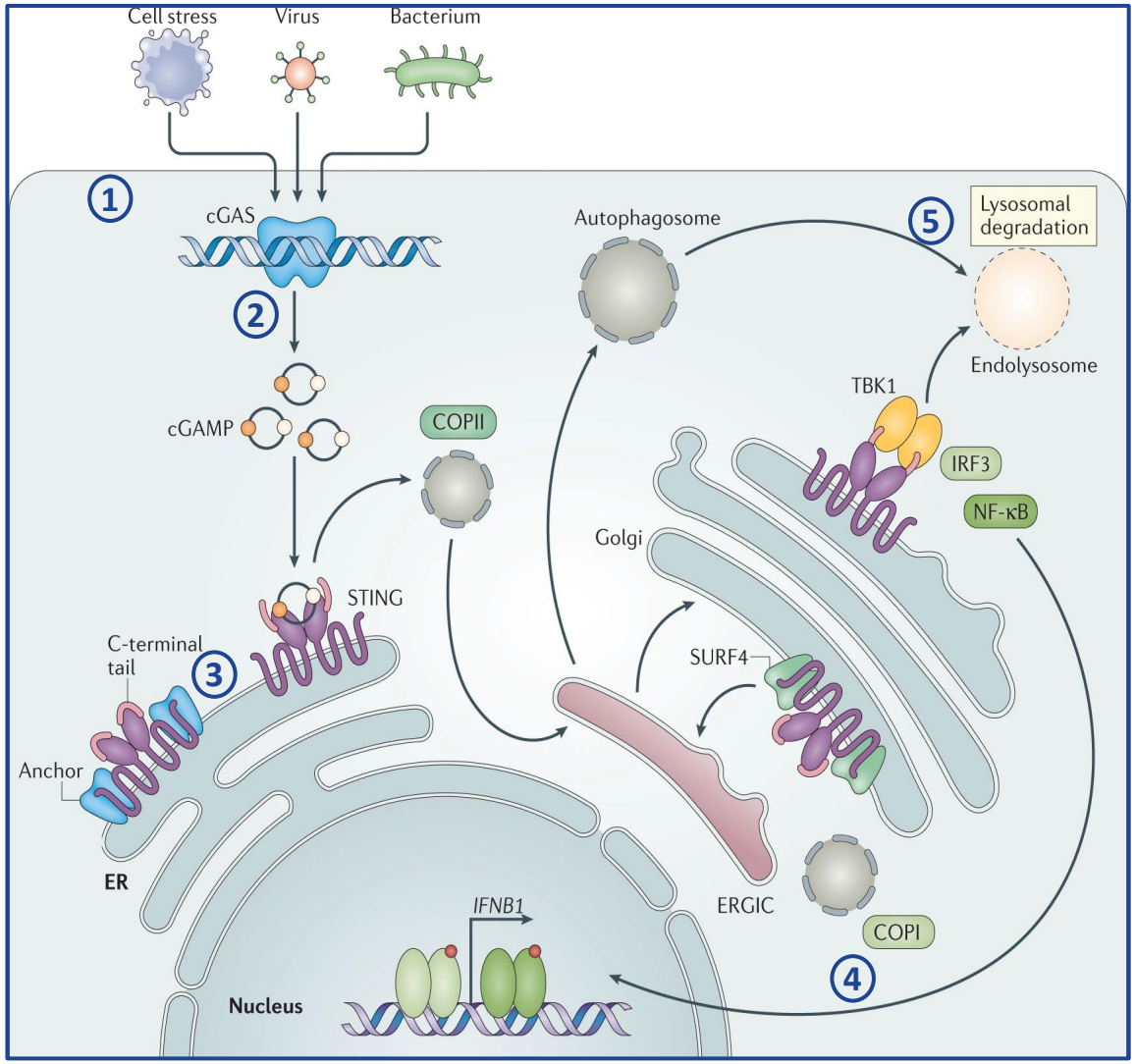
Regor Therapeutics Group

Stimulator of Interferon Genes (STING): A MASTER MEDIATOR FOR INNATE IMMUNE RESPONSE



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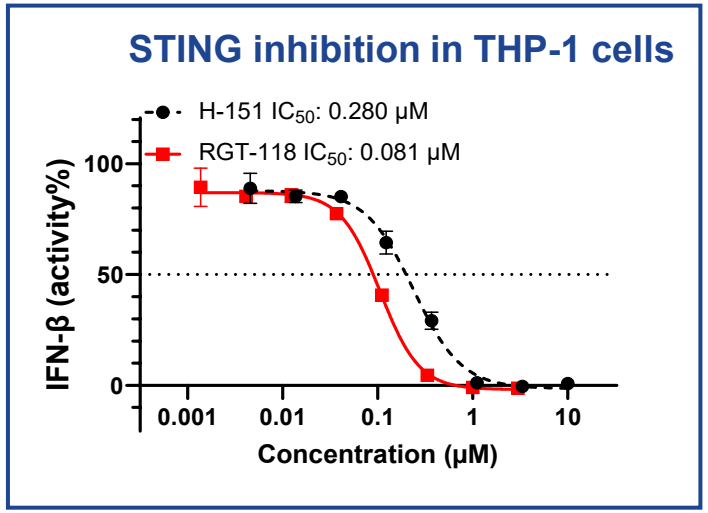
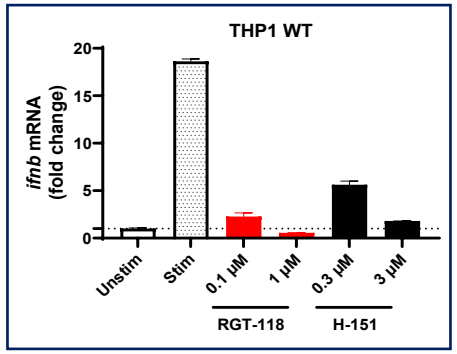
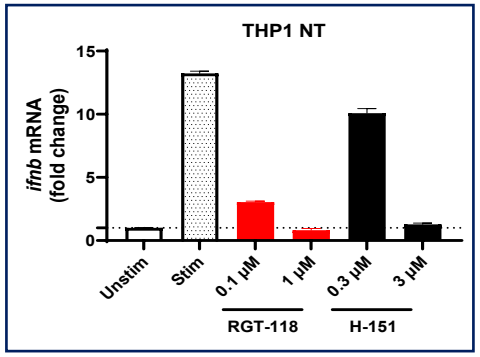
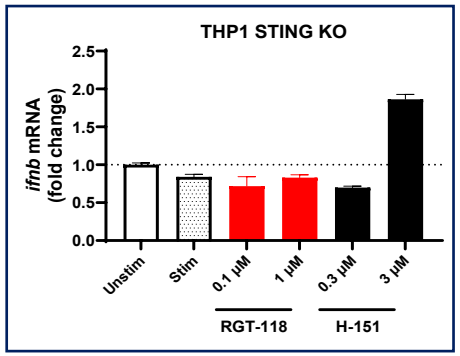
- cGAS-STING pathway as a key innate immune mediator senses self- and non-self DNA
- cGAS binds DNA and produces cGAMP, which activates STING-mediated immune signaling
- STING is activated on ER, signals after it translocates to Golgi and is degraded by the lysosome
- Therefore, STING antagonist can inhibit both ligand dependent and trafficking mediated disorders

RGT-118 SELECTIVELY INHIBITED cGAS-STING SIGNALING *IN VITRO*









NT: non-targeting gRNA

RGT-118 DOSE DEPENDENTLY SUPPRESSED cGAS-STING SIGNALING *IN VIVO*

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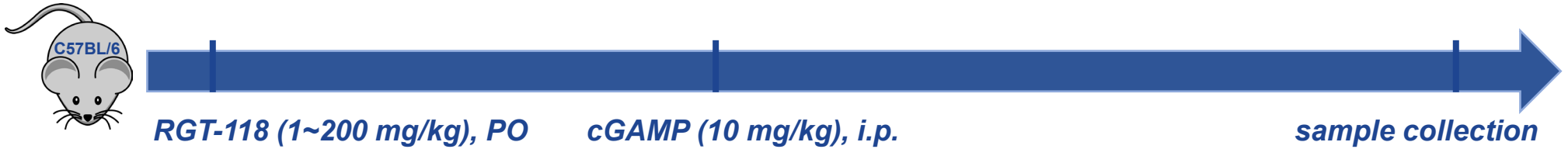

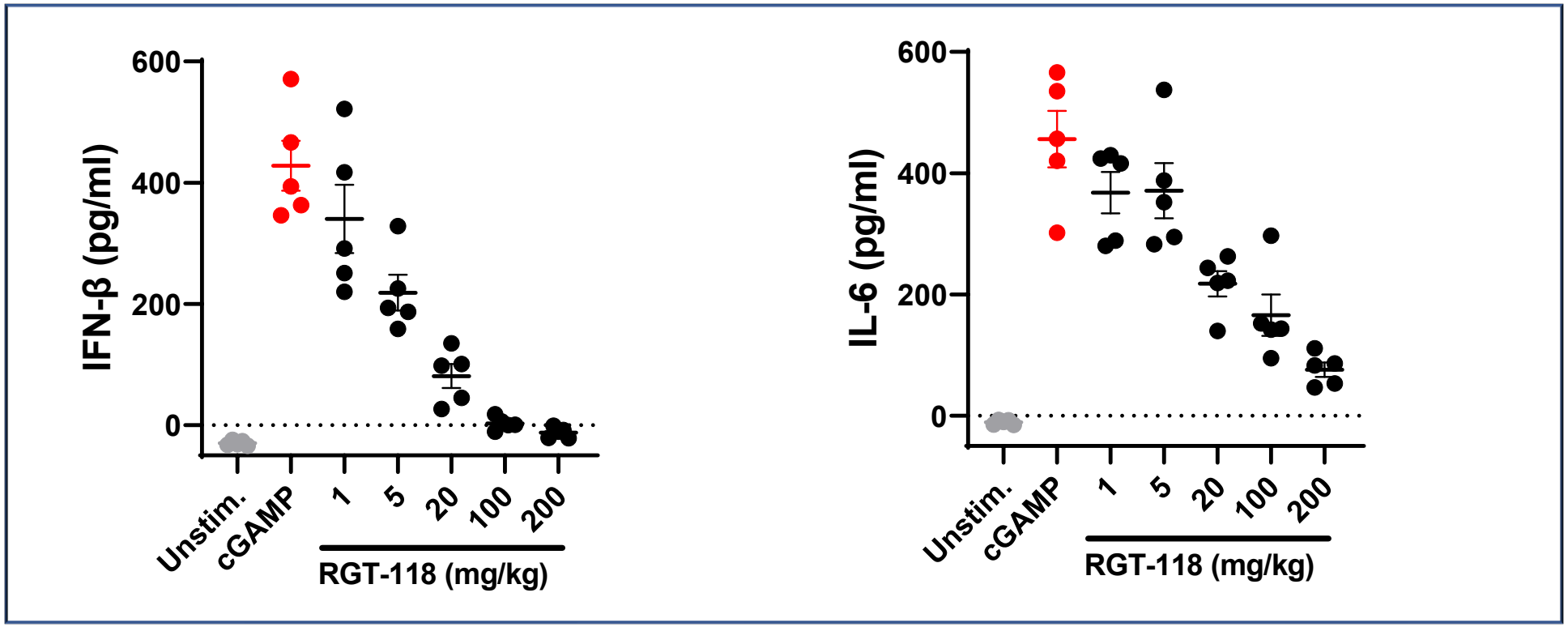

RGT-118 ALLEVIATED HEART INFLAMMATION IN TREX1$^{-/-}$ MICE

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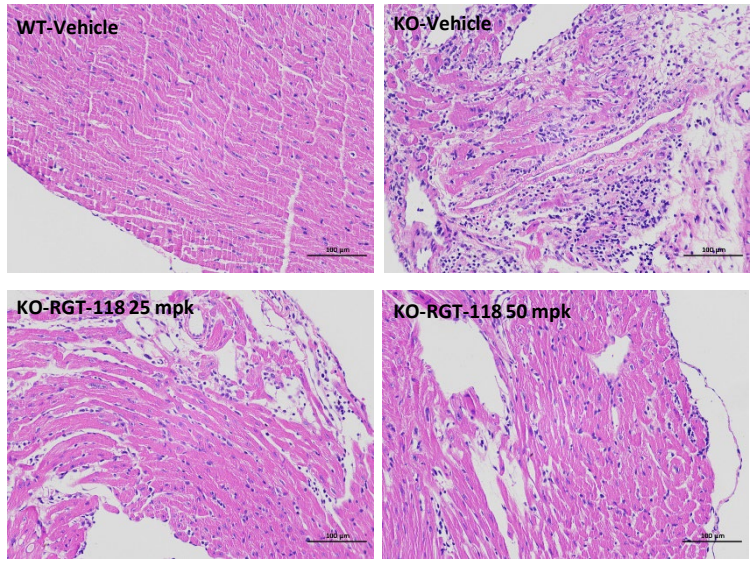
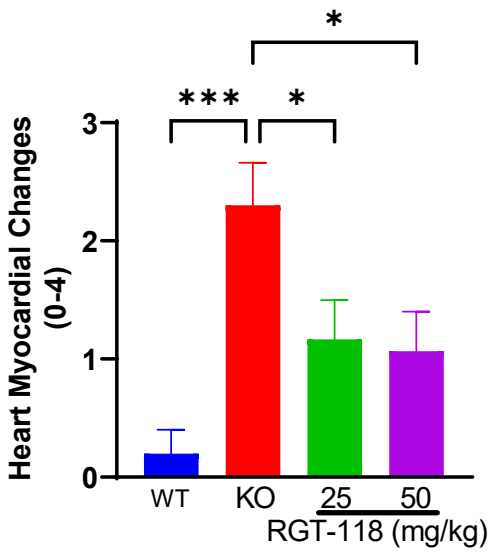
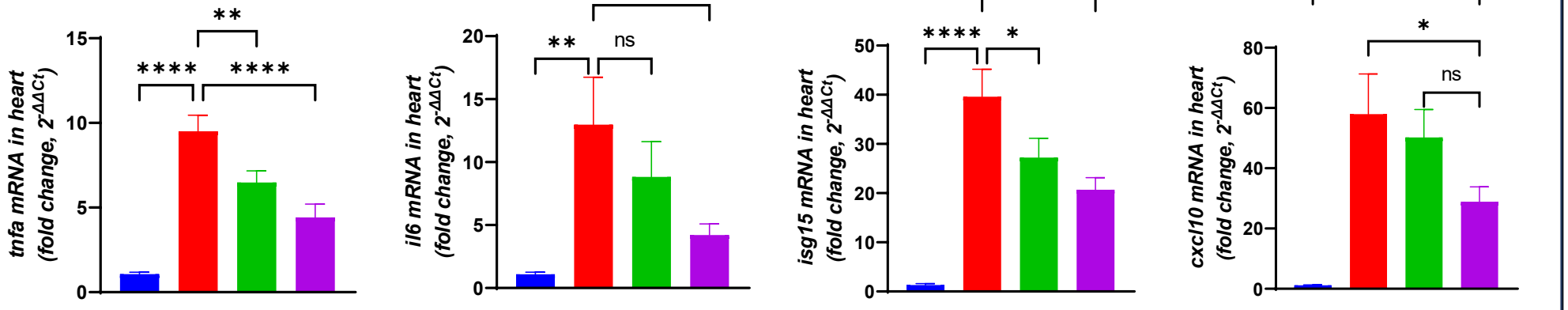




- RGT-118, dosed PO QD for 4 weeks, ameliorated heart damage in lupus-like Trex1$^{-/-}$ mice
- RGT-118 inhibited both NF-κB and type I IFN pathways in a dose-dependent manner



RGT-118 INHIBITED TYPE I IFN PATHWAY IN PSORIATIC SKIN

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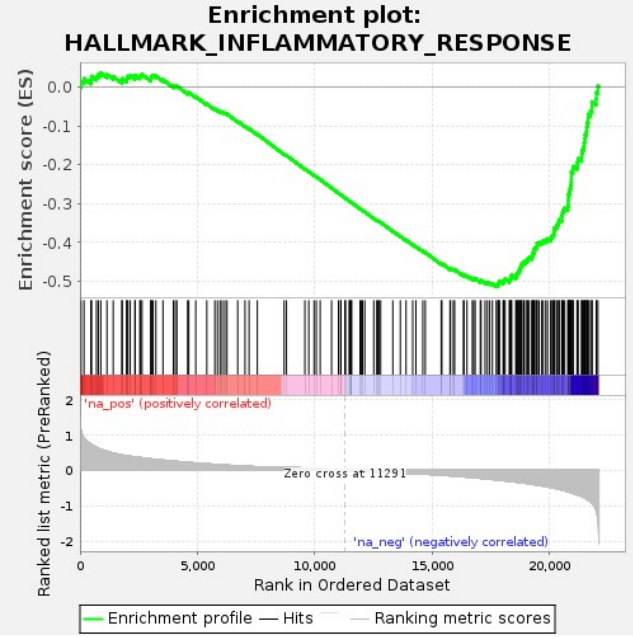
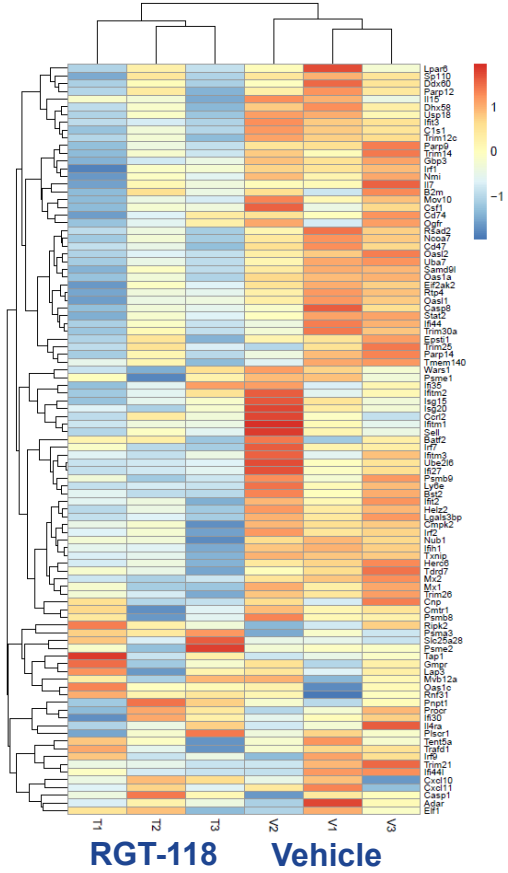
Day 0 → **Day 5**

AM: Scoring & Dosing
PM: IMQ immunization on back skin

RGT-118 treatment *vs* Vehicle



Skin RNA-Seq Analysis



OPPORTUNITY IN AUTOIMMUNE AND INFLAMMATORY DISEASES

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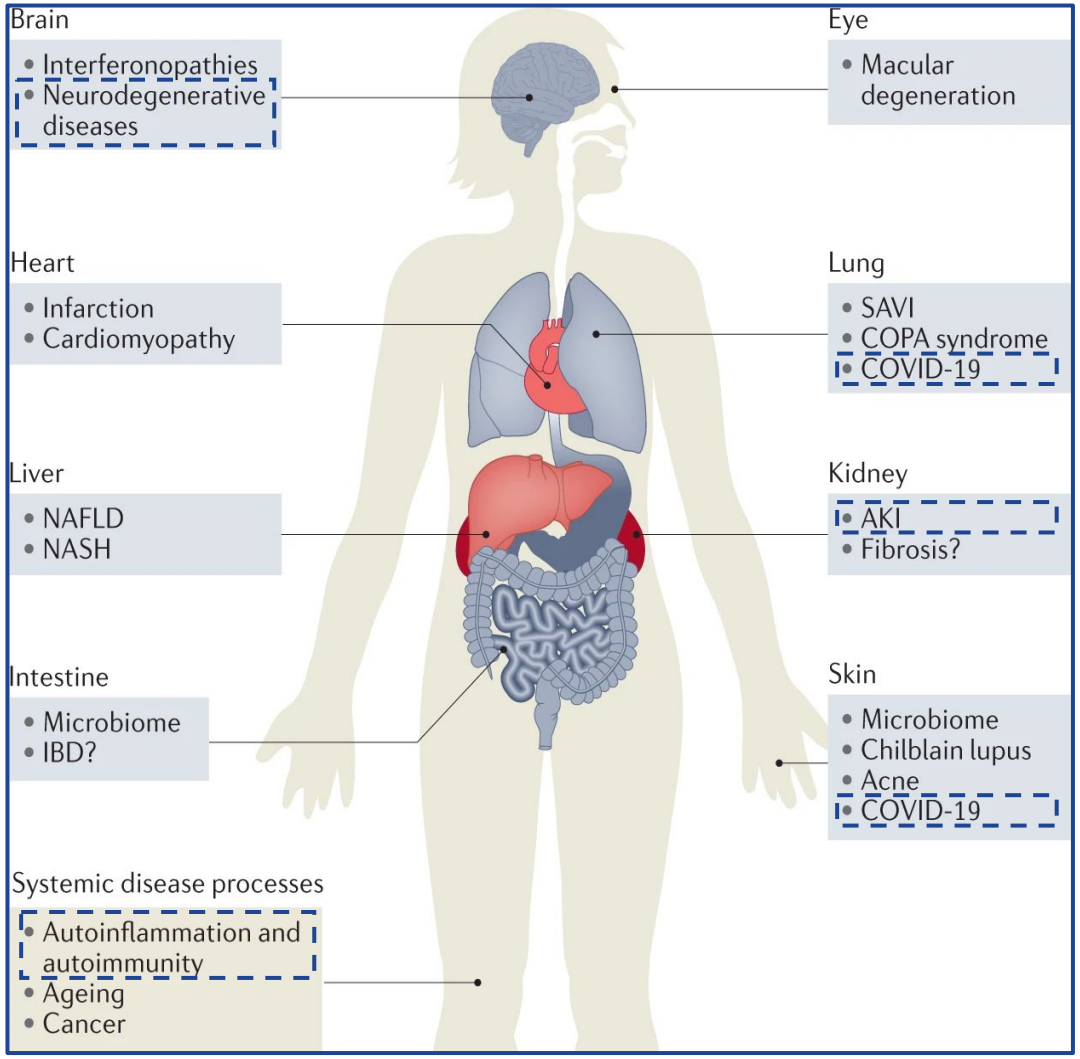

Ligand-dependent

- SLE
- Sjögren's Syndrome
- Psoriasis
- AKI
- Long COVID
- Inflammaging

Trafficking-dependent

- ALS*
- NPC

** CSF exposure of RGT-118 was observed*

Nat Rev Nephrol 2022 https://doi.org/10.1038/s41581-022-00589-6

SUMMARY

- **Indication:** Autoimmune and inflammatory diseases
- **Preclinical POC:** RGT-118 has been identified as a potent, selective and orally bioavailable small molecule STING antagonist with brain penetrant potential. RGT-118 inhibited cGAMP-induced downstream STING signaling in a dose-dependent manner *in vitro* and *in vivo.* RGT-118 alleviated heart inflammation in Trex1$^{-/-}$ GEMM model and demonstrated therapeutic activities in autoimmune models such as IMQ-induced psoriasis model.
- **Status:** Preclinical characterization including the 14-day exploratory toxicity data in rats and dogs supports its further development.
- **Value Proposition:** RGT-118 provides first-in-class opportunity of an orally bioavailable small molecule STING antagonist with a novel MOA to treat patients with autoimmune and inflammatory diseases.

ACCELERATED DISCOVERY BREAKTHROUGH MEDICINES

Thank you!

Looking Forward to Collaboration!

CARD
Computer Accelerated Rational Discovery

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