

Inhibitors of Endogenous Reverse Transcriptases Suppress *in vitro* Type I Interferon Responses and *in vivo* Antigen-specific T cell Responses

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Disclosure

- I am an employee of ROME Therapeutics, Inc.

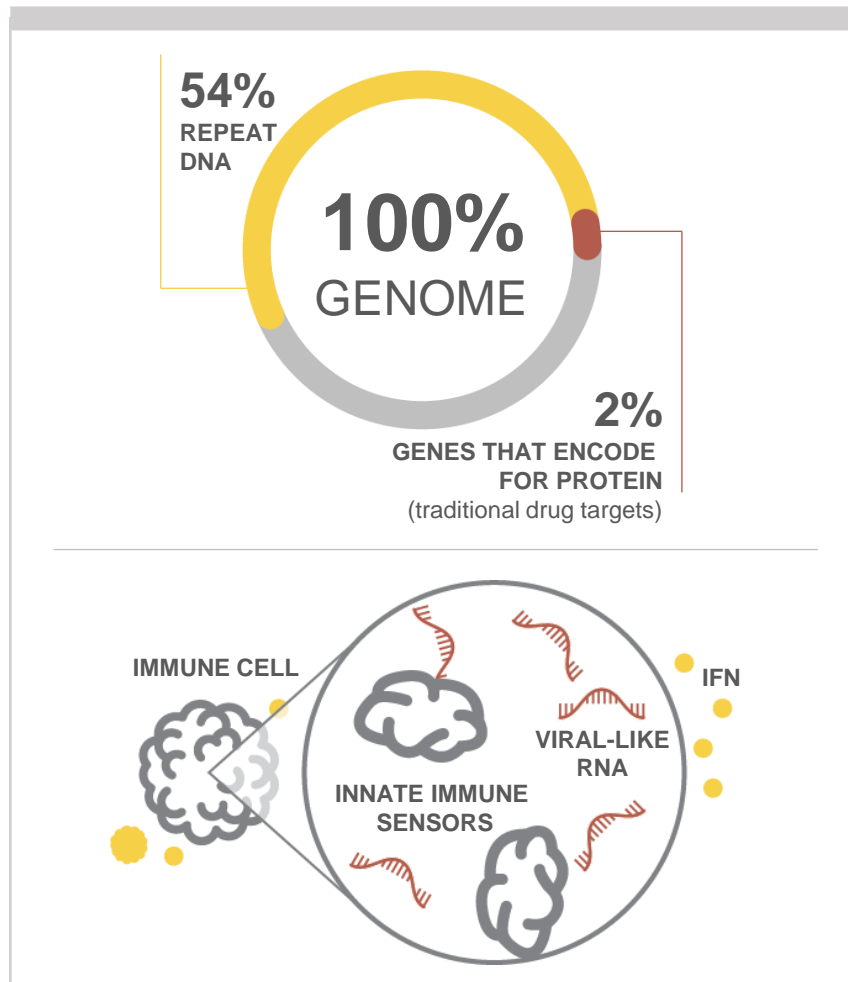
Evidence-Based Medicine (EBM) or Key References

- Rice GI, et al. **Reverse-Transcriptase Inhibitors in the Aicardi–Goutières Syndrome.** *New England Journal of Medicine*, 2018, 379: 2275

- Gorbunova V et al. **The Role of Retrotransposable Elements in Ageing and Age-associated diseases.** *Nature*, 2021, 596:43

- Ukadike KC, et al. **Implications of Endogenous Retroelements in the Etiopathogenesis of Systemic Lupus Erythematosus.** *Journal of Clinical Medicine*, 2021, 10: 856

The Repeatome Plays a Critical Role in Human Health and Disease



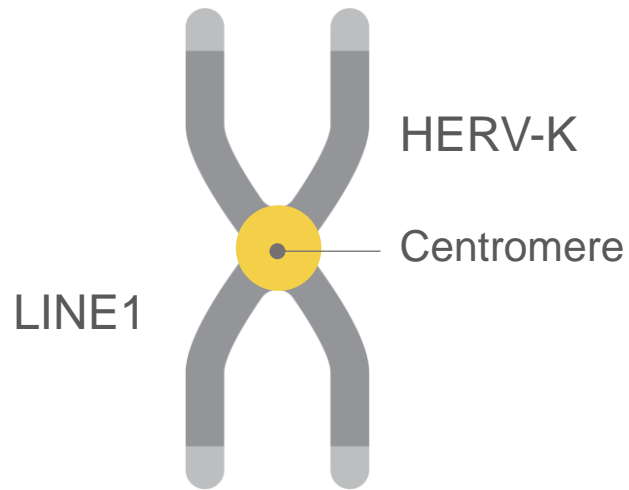
Repeats are repetitive nucleic acid sequences derived from viruses that have integrated into our DNA during evolution

Repeats remain mostly dormant in healthy cells. When cells are sick or injured, repeats are activated and elicit a “viral mimicry” response by engaging immune sensors

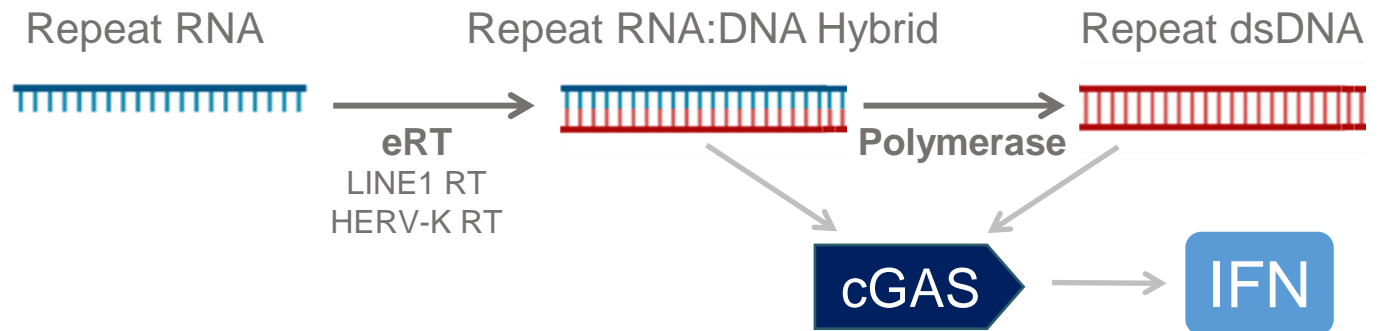
When co-opted, repeat reactivation has pathological consequences in cancer, autoimmunity and neurodegeneration

Endogenous Reverse Transcriptases (eRTs) Encoded by Repeats Activate Innate Immune Responses

A subset of **LINE1** and **HERV-K** repeats encode functional eRTs



The products of eRTs trigger activation of the cGAS pathway



LINE1 – the most common endogenous retrotransposon

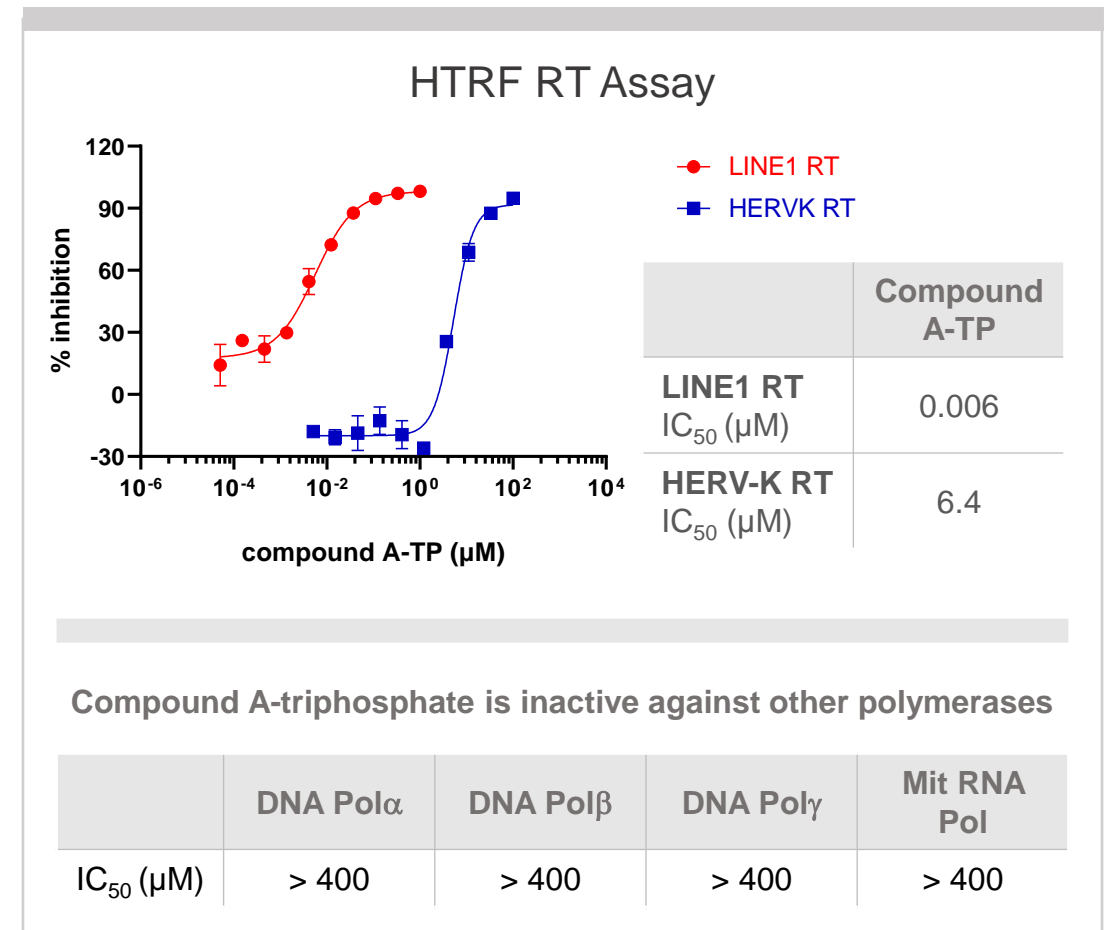
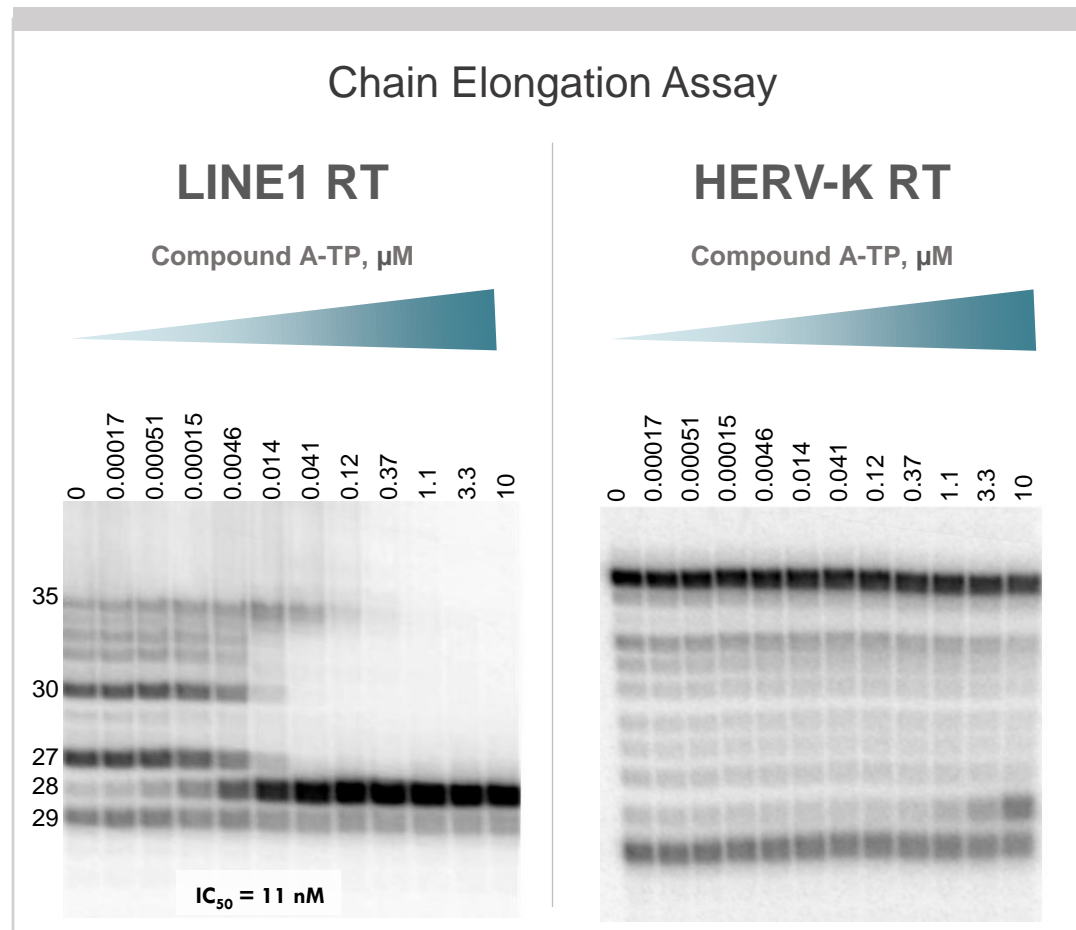
– About 100 LINE1 repeats encode a functional eRT

HERV-K – the most recently integrated endogenous retrovirus

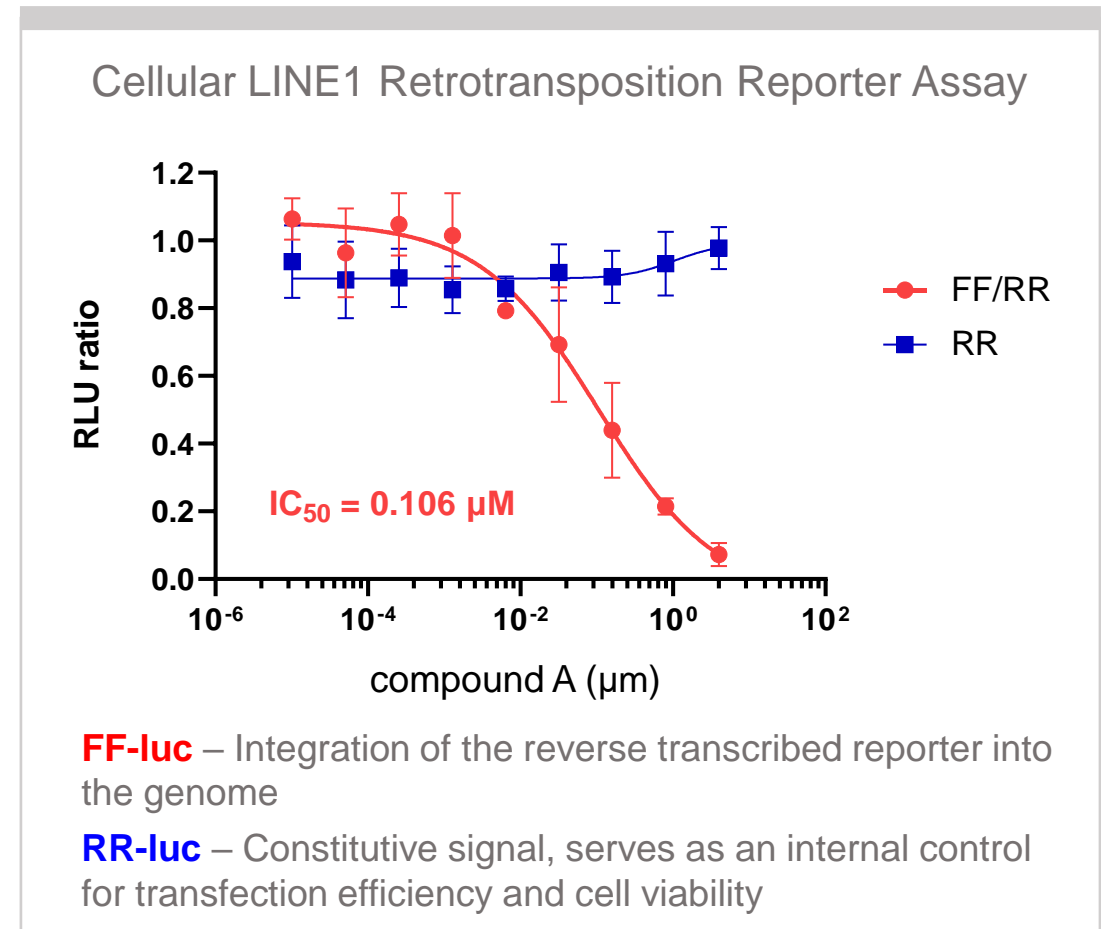
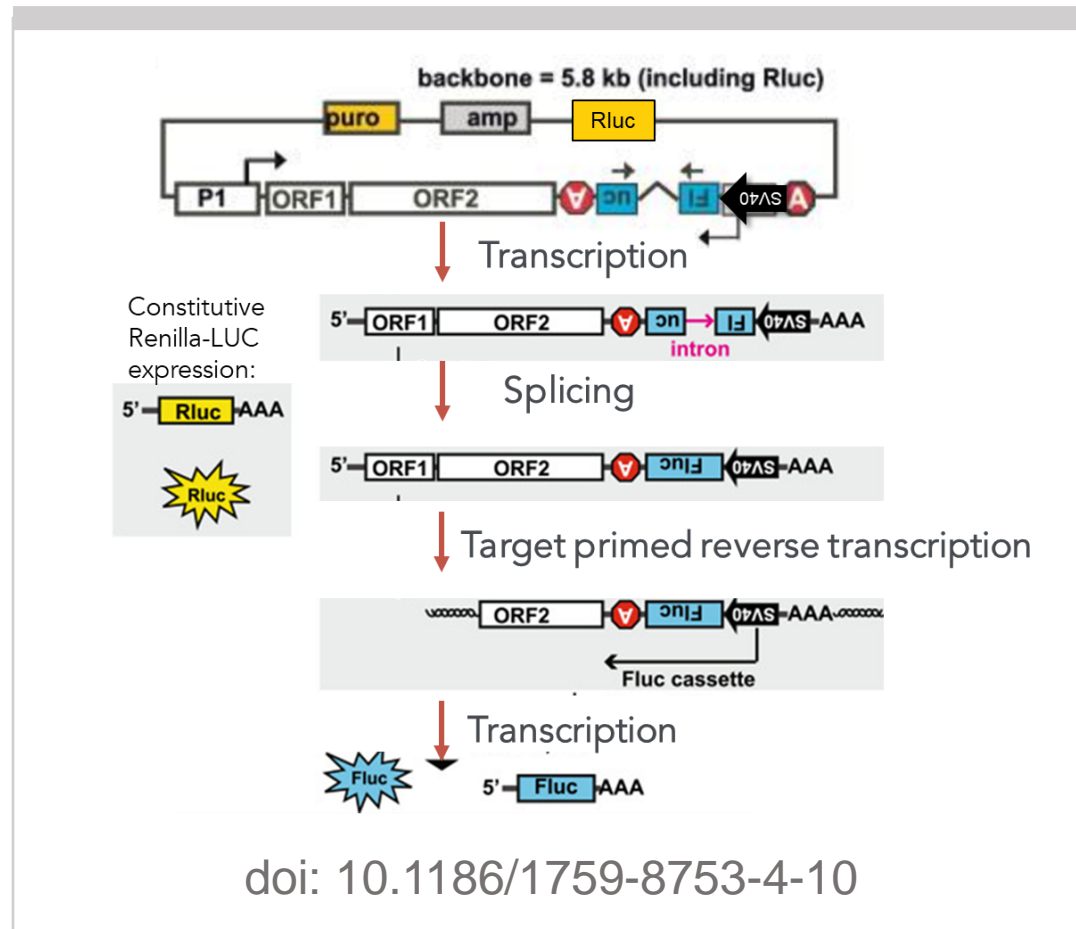
– About 60-80 HERV-K repeats encode a functional eRT

Compound A is a Potent and Selective eRT Inhibitor

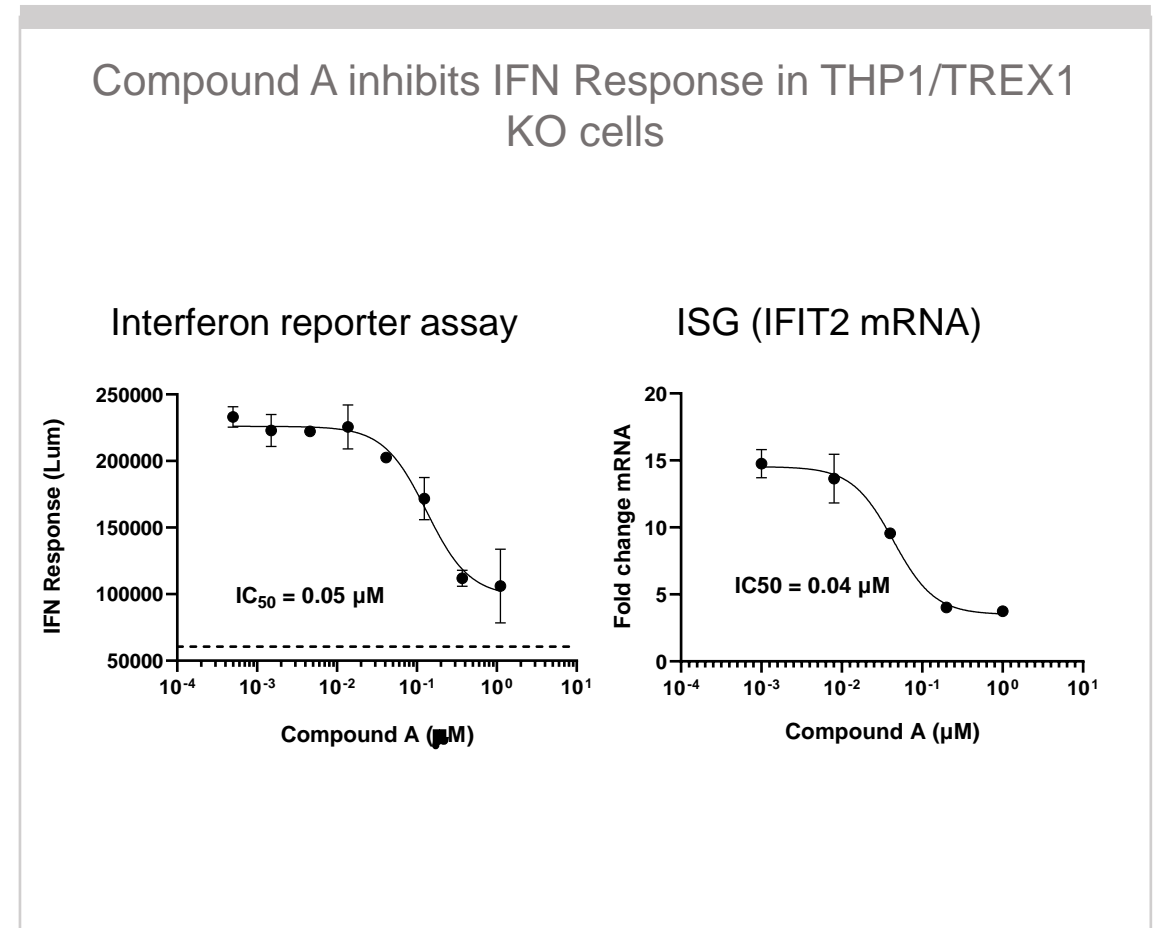
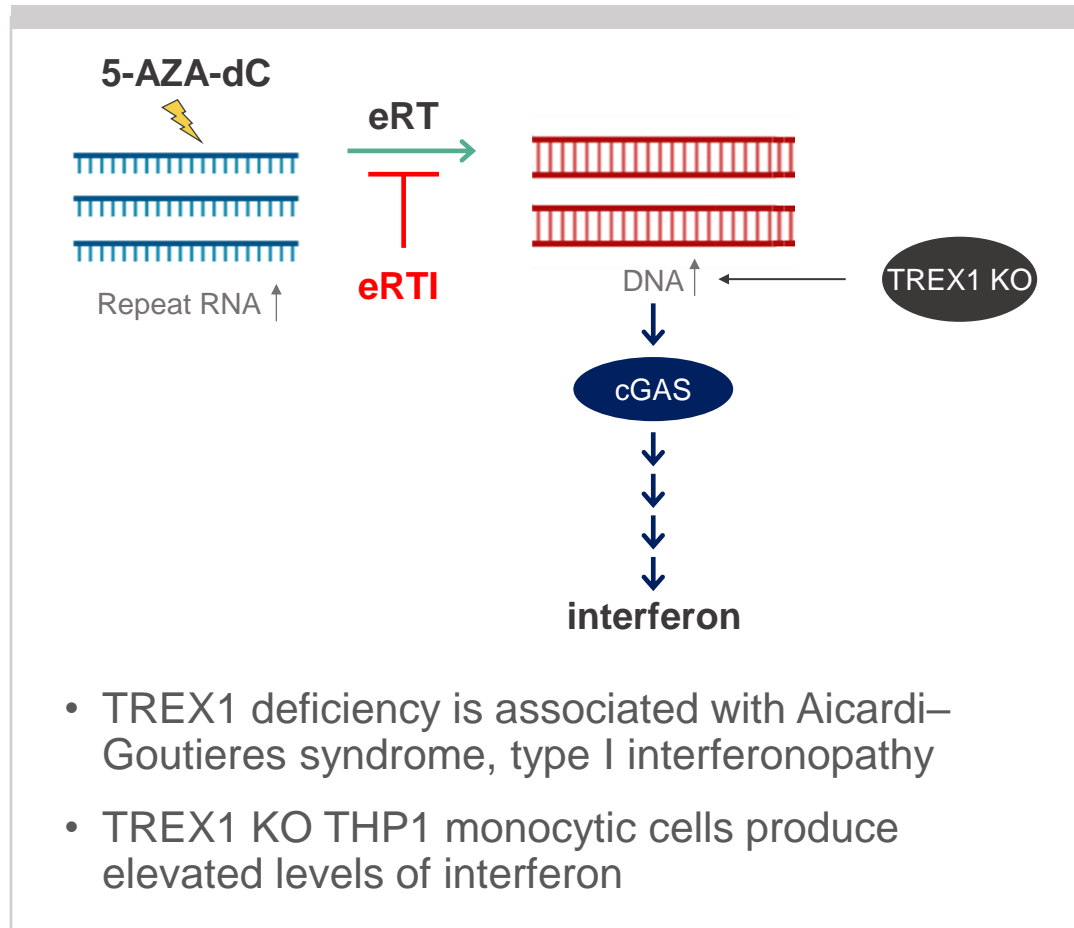
Compound A-triphosphate inhibits eRT activity in biochemical assays



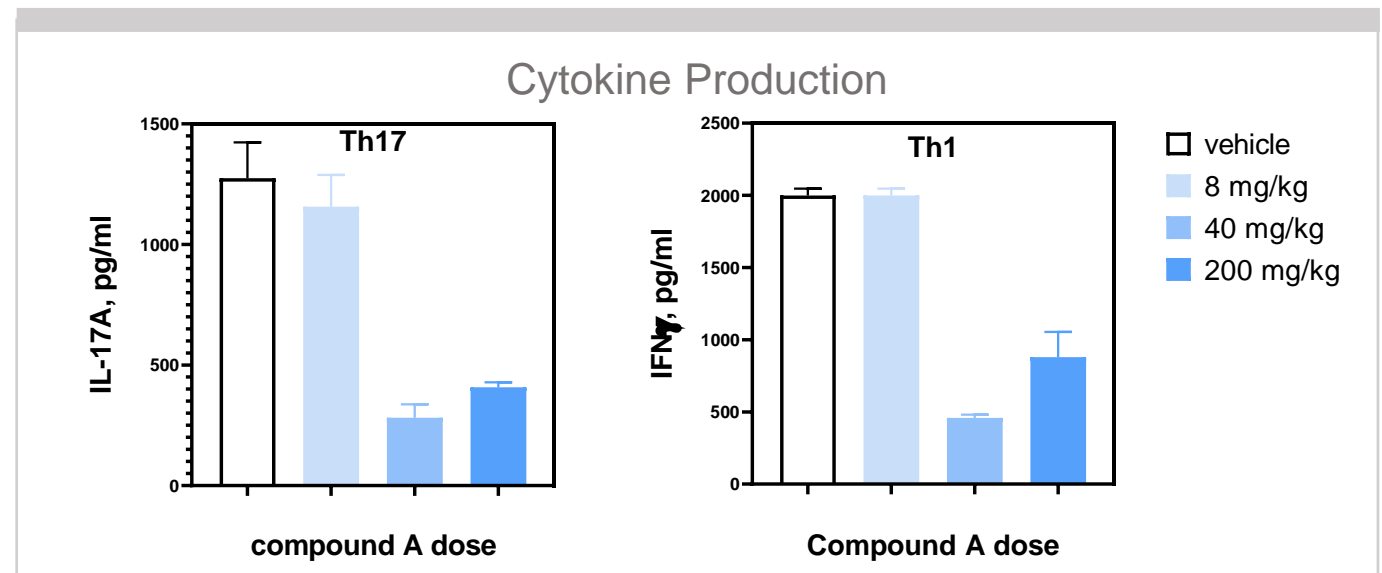
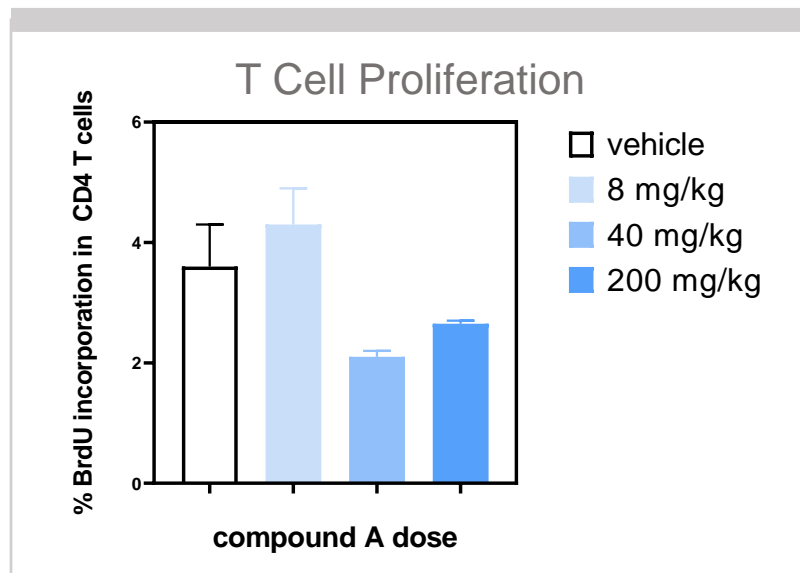
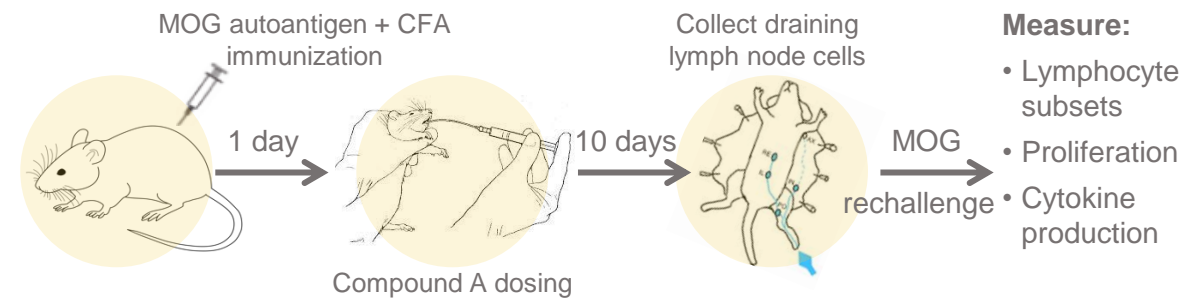
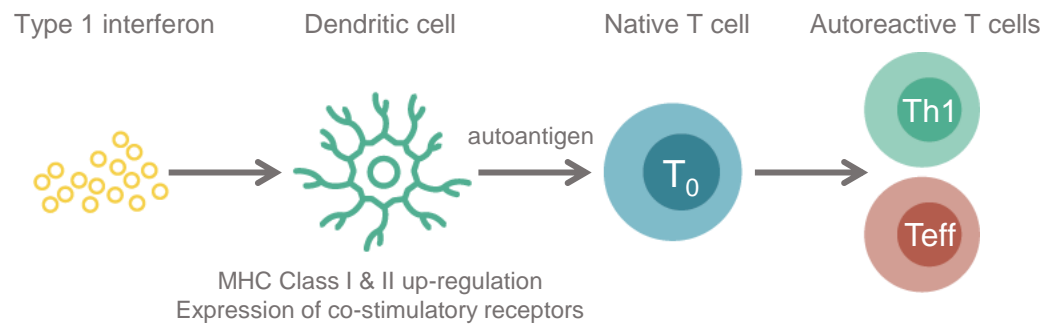
Compound A Inhibits LINE1 Retrotransposition in a Cellular Assay



Compound A Inhibits Type I Interferon Response in a Cellular Model of Aicardi–Goutières Syndrome



Compound A Attenuates Antigen-specific T cell Responses in MOG-immunized mice



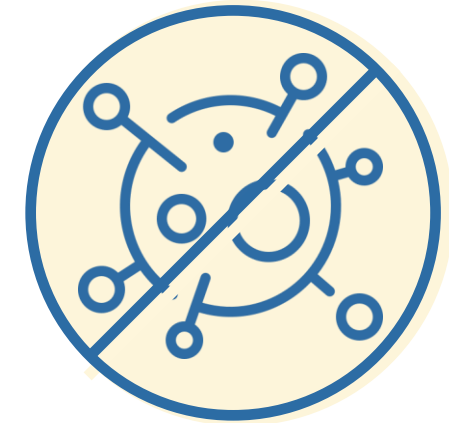
eRT Inhibitors are Promising Therapeutics for Treating Type I Interferonopathies



Potent and **selective inhibitor** of eRT activity



Abolishes LINE1 retrotransposition



Suppresses type I interferon responses by innate sensing