#7946 Identification of a highly selective ITK inhibitor which promotes Th1 differentiation and alleviate T cell exhaustion *in vitro* and *in vivo*

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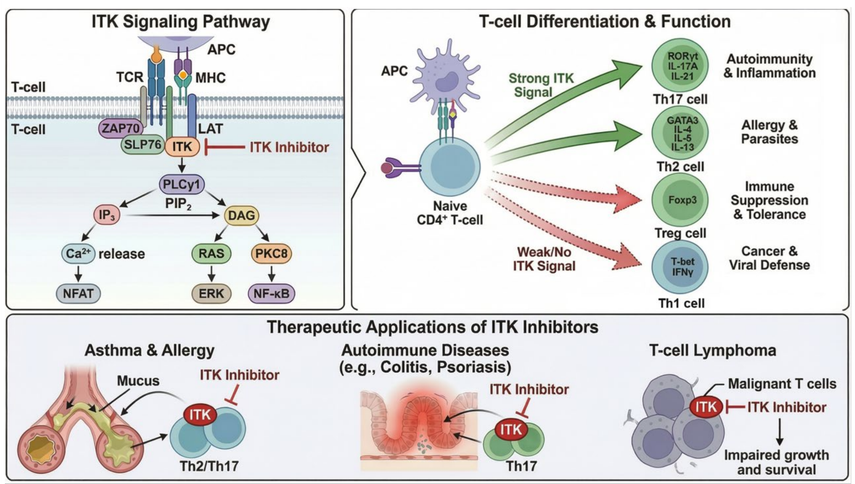
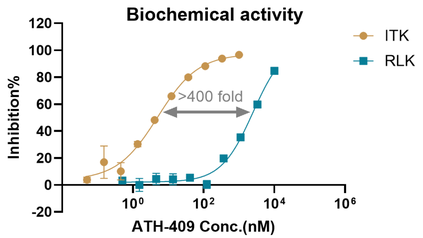
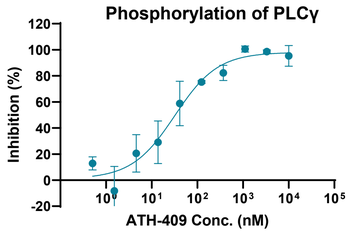
Introduction

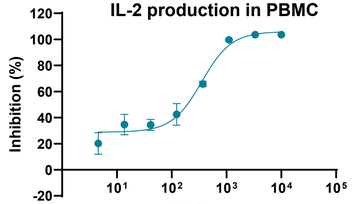
- IL-2-inducible T-cell kinase (ITK), a member of the TEC family, plays a critical role in T cell signal transduction and T cell differentiation. Resting lymphocyte kinase (RLK), another TEC family kinase, exhibits functional redundancy with ITK and is preferentially involved in Th1 differentiation.
- ITK knockout mice show defects in Th2 differentiation, while retaining the ability to differentiate into Th1 cells. Double knockout of ITK and RLK in T cells induces a more substantial signaling defect, resulting in a profound loss of normal T cell function. These findings suggest that developing ITK inhibitors sparing RLK activity could serve as a potential target for T cell lymphoma and Th2-related disease.
- ATH-409, a highly selective covalent ITK inhibitor, robustly suppresses ITK activity and inhibits the phosphorylation of PLCγ1, leading to blockage of TCR activation-induced IL-2 release. It demonstrates inhibitory effects on the proliferation of human pan-T cell and Th2 differentiation, but displays a weak effect on Th1 differentiation. It shows good selectivity against 430 kinases, including 10 cysteine-containing kinases.

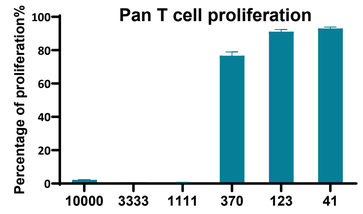


Effect on ITK signaling and T cell function



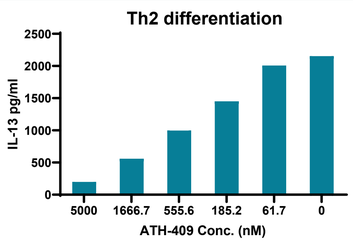


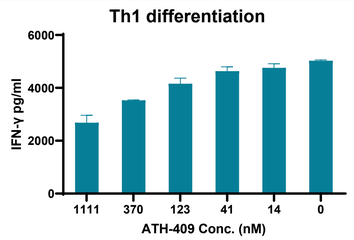


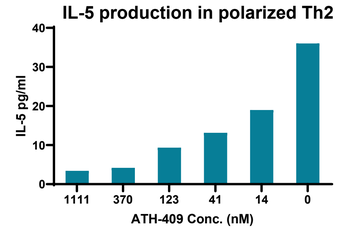


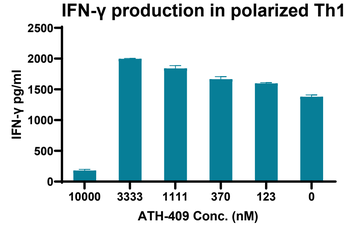
- ATH-409, a selective ITK inhibitor, sparing RLK activity, potently inhibited the phosphorylation of PLCγ1 and furtherly blocked TCR-induced IL-2 production and proliferation.

Effect on Th1/Th2 differentiation



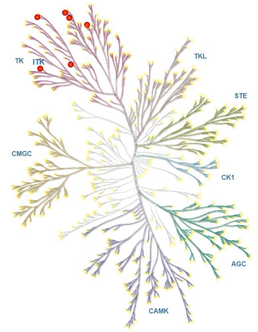






- ATH-409 strongly suppresses Th2 differentiation and the release of the Th2 cytokine, while showing minimal effect on Th1 differentiation and Th1 cytokine production.

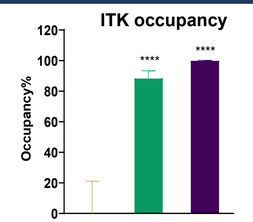
Kinase selectivity

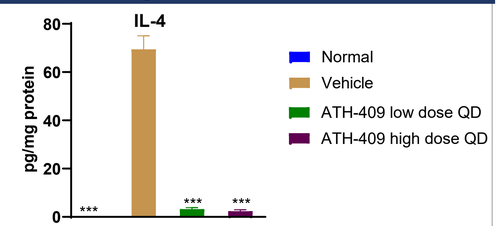


Cystine containing kinases	ATH-409	Selectivity fold
ITK	4.9	1.0
BLK	3023.4	617.0
BMX	>10000	>2040
BTK	2441.5	498.3
EGFR	>10000	>2040
ErbB2	>10000	>2040
ErbB4	>10000	>2040
JAK3	7586.2	1548.2
MKK7	>10000	>2040
TEC	625.2	127.6
RLK	2132.7	435.2

- ATH-409 exhibits off-target potency against 5 of 430 kinases with inhibitory rates greater than 90% at 3 μM. It displays at least 100-fold selectivity against the remaining 10 cysteine-containing kinases.

ITK occupancy *in vivo*





- ATH-409 achieves near complete ITK occupancy at 2h after drug treatment. Furtherly, it demonstrates robust inhibitory effect on Th2 cytokine release in tissue *in vivo*.

Summary

- ATH-409 is a potent selective ITK inhibitor, sparing RLK activity. It potently blocks TCR signaling, leading to inhibition of Th2 differentiation and Th2 cytokines release *in vitro* and *in vivo*. These findings support ITK as a promising target for T cell lymphoma and Th2-related disease.

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