EMPOWERING PATIENTS THROUGH KINOME INNOVATION

Overview of ITK Portfolio

May 7, 2024

aclaris® THERAPEUTICS

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Any statements contained in this presentation that do not describe historical facts may constitute forward-looking statements as that term is defined in the Private Securities Litigation Reform Act of 1995. These statements may be identified by words such as “anticipate,” “believe,” “expect,” “intend,” “may,” “plan,” “potential,” “will,” and similar expressions, and are based on Aclaris’ current beliefs and expectations. These forward-looking statements include expectations regarding the development of ATI-2138, including the commencement of a Phase 2a clinical trial, and the development of a next-generation ITK selective inhibitor. These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements. Risks and uncertainties that may cause actual results to differ materially include uncertainties inherent in the conduct of clinical trials, Aclaris’ reliance on third parties over which it may not always have full control, Aclaris’ ability to enter into strategic partnerships on commercially reasonable terms, the uncertainty regarding the macroeconomic environment and other risks and uncertainties that are described in the Risk Factors section of Aclaris’ Annual Report on Form 10-K for the year ended December 31, 2023, and other filings Aclaris makes with the U.S. Securities and Exchange Commission from time to time. These documents are available under the “SEC Filings” page of the “Investors” section of Aclaris’ website at www.aclaristx.com. Any forward-looking statements speak only as of the date of this presentation and are based on information available to Aclaris as of the date of this presentation, and Aclaris assumes no obligation to, and does not intend to, update any forward-looking statements, whether as a result of new information, future events or otherwise.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about our industry. These data involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

ATI-2138: A First Generation Novel ITK/JAK3 Inhibitor for T Cell-Mediated Diseases

(Investigational Drug Candidate)

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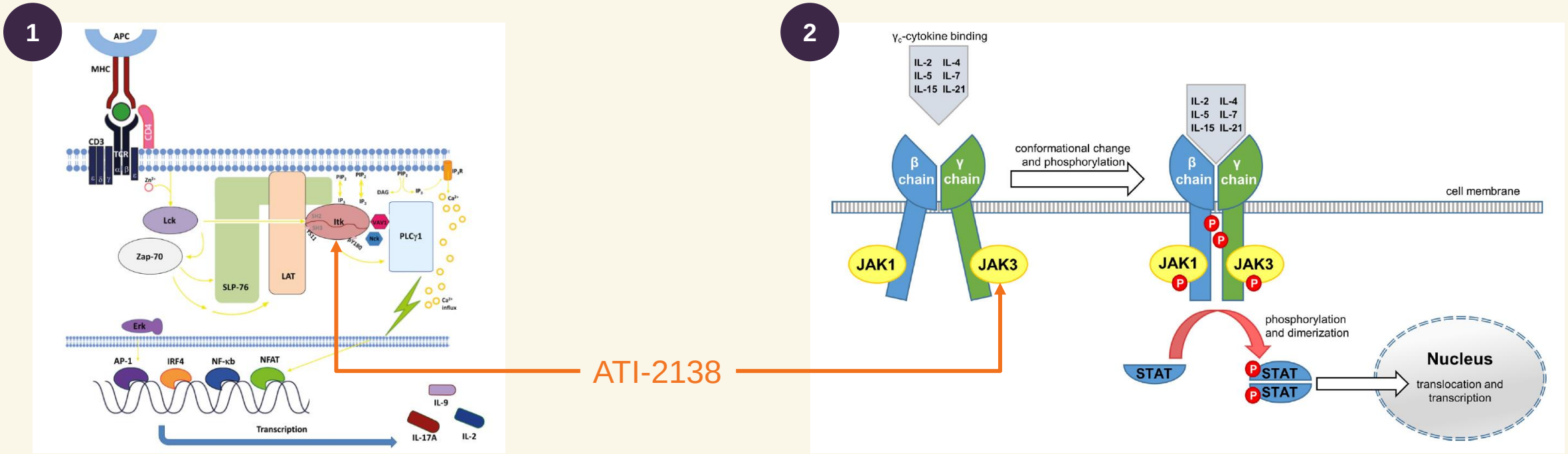
ATI-2138 is a Combined Covalent IL-2-Inducible Tyrosine Kinase (ITK) & JAK3 Inhibitor for Autoimmune Disease

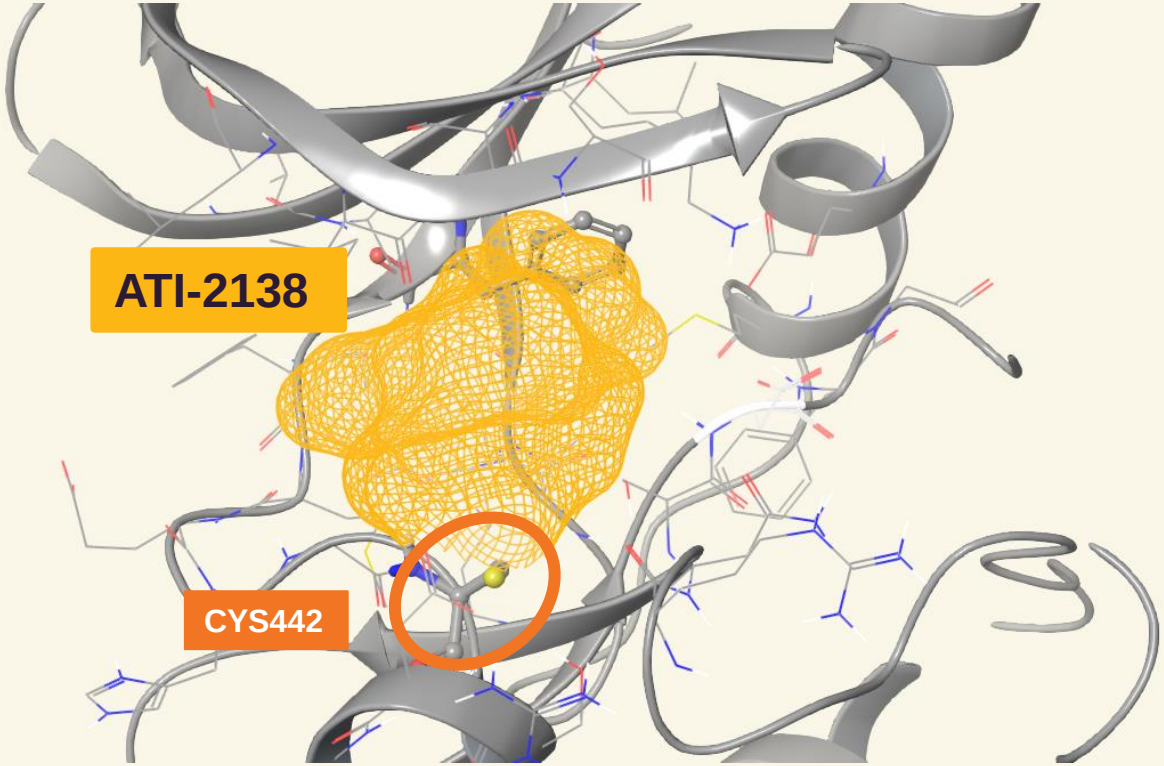


- ATI-2138 is an investigational oral compound which interrupts T cell receptor (TCR) signaling by inhibiting ITK and JAK3 signaling of common γ chain cytokines in lymphocytes (including IL-2 & IL-15) and is designed to reduce T cell differentiation, proliferation and cytokine production
- ATI-2138 is differentiated from other kinase inhibitors as it is highly potent for both ITK and JAK3 (IC50: 0.2nM ITK; 0.5nM JAK3)[3]
- Aclaris is evaluating ATI-2138 for the potential treatment of a number of T cell-mediated autoimmune diseases including atopic dermatitis

1. Lechner KS, Neurath MF, Weigmann B. Role of the IL-2 inducible tyrosine kinase ITK and its inhibitors in disease pathogenesis. J Mol Med (Berl). 2020 98(10):1385-1395; 2. Forster M, Gehringer M, Laufer SA. Recent advances in JAK3 inhibition: Isoform selectivity by covalent cysteine targeting. Bioorg Med Chem Lett. 2017 15;27(18):4229-4237; 3. Study Report SR03001

ATI-2138 Covalently Inhibits ITK and JAK3

ATI-2138 was designed to interact with the ATP site and covalently modifies CYS442 in ITK and CYS909 in JAK3



- Design guided by modeling and proprietary crystal structures
- ATI-2138 modeled into ITK kinase domain 3QGY
- ATI-2138 interacts with CYS909 in JAK3

- Other oral drugs have successfully targeted these cysteines in kinases
  - Ritlecitinib (JAK3), Ibrutinib (BTK)
  - Afatinib, Neratinib (EGFR/Her2)

ATI-2138: Potential for Meaningful Differentiation

ATI-2138, by modulating both TCR signaling (via ITK blockade) and cytokine signaling (via JAK3 blockade), is a T cell focused modulator and potentially ideal for treating autoimmune diseases with high unmet medical need

Cell IC_{50}, nM	**ITK** (Jurkat/pPLCγ1)	**JAK3** hPBMC IL-2/pSTAT5	**JAK1/2** hPBMC IFNγ/pSTAT1
ATI-2138	8 *(81-fold)*	23 *(2.3-fold)*	*Inactive*
Tofacitinib	*Inactive*	11	205
Ritlecitinib	652	54	*Inactive*

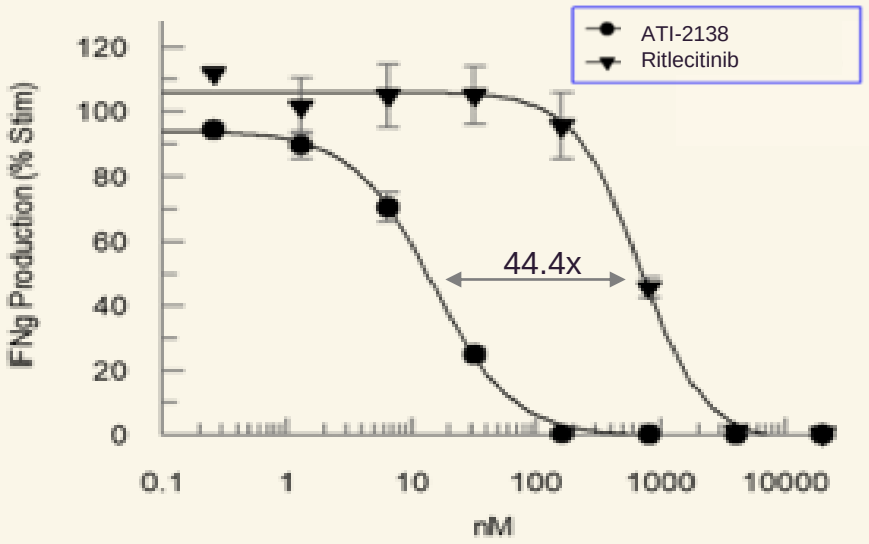
ATI-2138 differs from both JAK inhibitors and ritlecitinib in important ways:

- Unlike approved JAK inhibitors, ATI-2138 is specific for JAK3 – does not inhibit other JAKs, including JAK2 which can lead to anemia
- Although both ATI-2138 and ritlecitinib are selective for JAK3, ATI-2138's potency on ITK is 20-80X greater than ritlecitinib

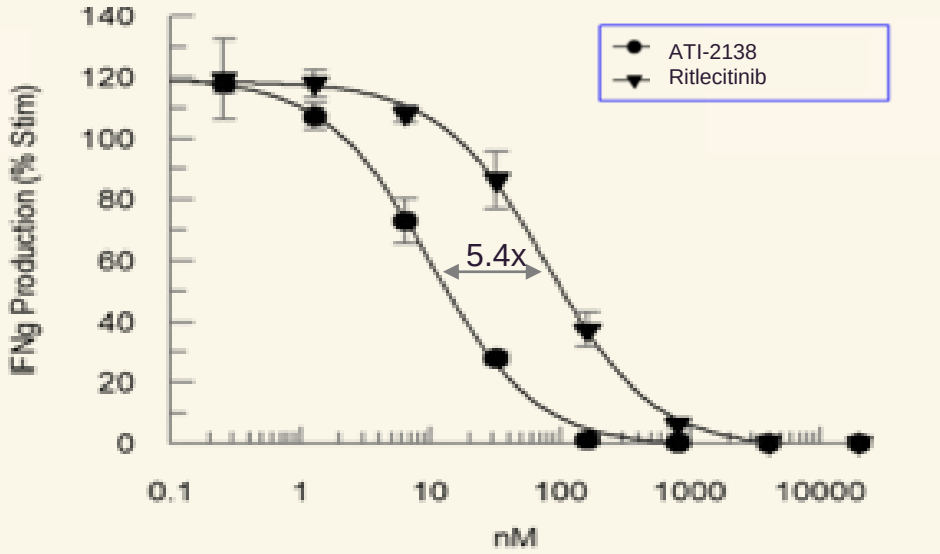
ATI-2138 Differentiation from Ritlecitinib

Dual ITK and JAK3 Inhibitors

ITK: HWB αCD3 Stimulated IFNγ Release



JAK3: HWB IL2 Stimulated IFNγ Release

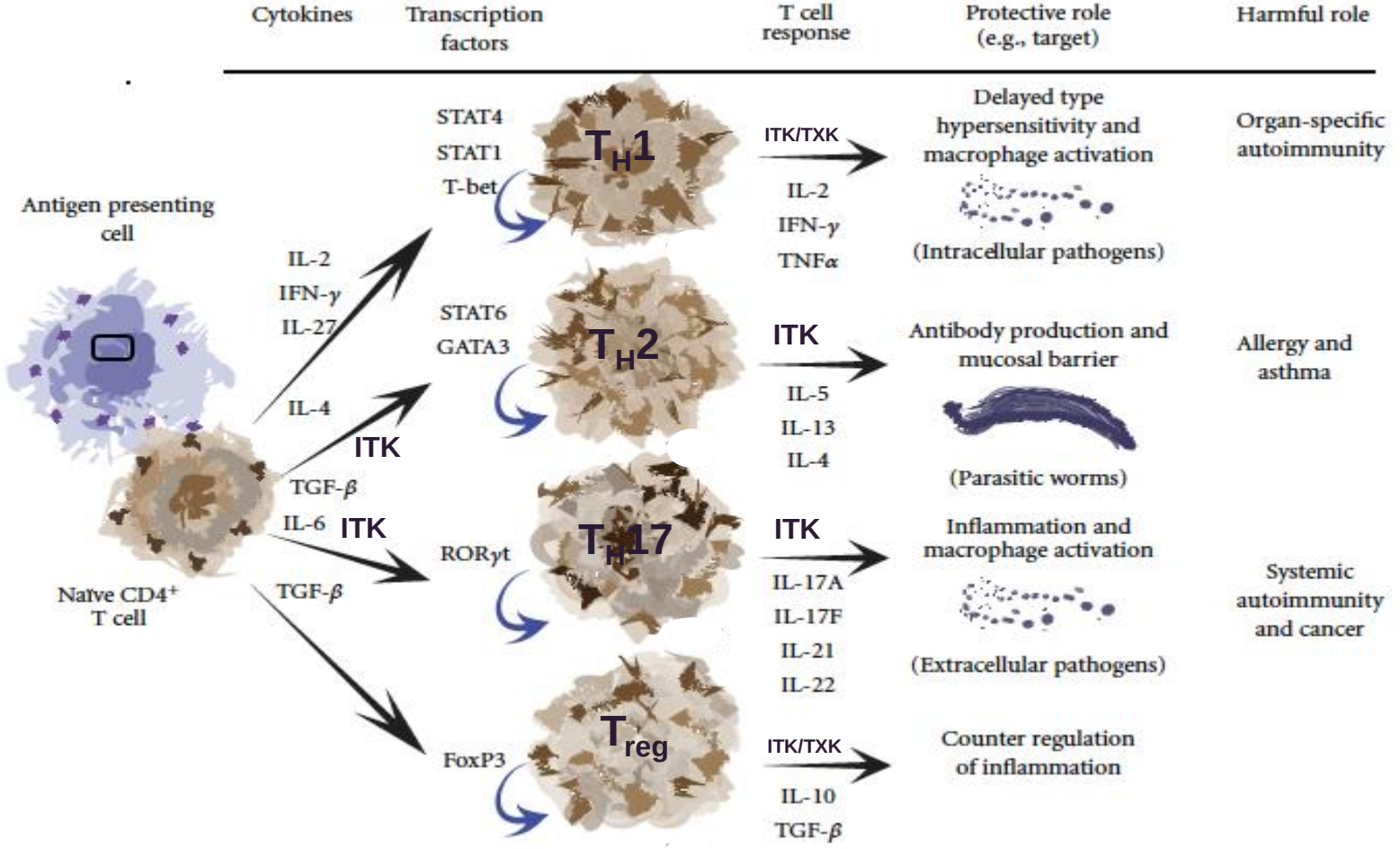


- ATI-2138 is 44.4x more potent than ritlecitinib for inhibiting αCD3 induced IFNγ production (ITK) and 5.4x more potent for inhibiting JAK3 dependent IL-2 induced IFNγ production in human whole blood
- At the FDA recommended 50 mg QD dose for alopecia areata, ritlecitinib plasma levels may not impact the anti-CD3 /IFNγ IC_{50} for any appreciable time
- In the ATI-2138 MAD study, the 5-40 mg BID doses inhibited up to 50%-90% of both ITK and JAK3 PD markers

ITK Modulates T Cell Differentiation and Activation

Skews T Helper Cell Differentiation Towards Th2 and Th17 Phenotypes

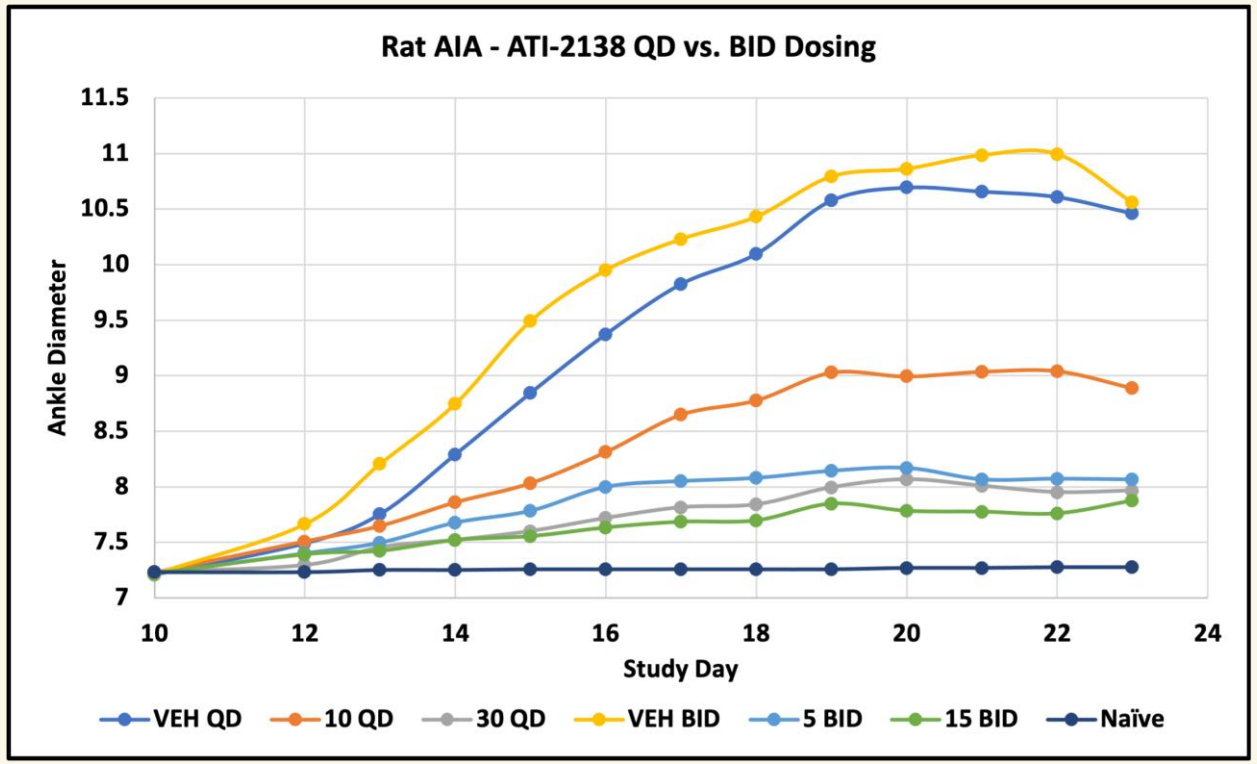
- ITK has a nonredundant role in the differentiation and activation of T_H2 and T_H17 cells
- Knockdown or inhibition of ITK in mice and humans results in skewing of T helper cells from T_H2 and T_H17 toward T_H1 and T_{reg}
- Blockade of T_H2 function inhibits production of IL-4 and IL-13, two cytokines with demonstrated importance in atopic diseases

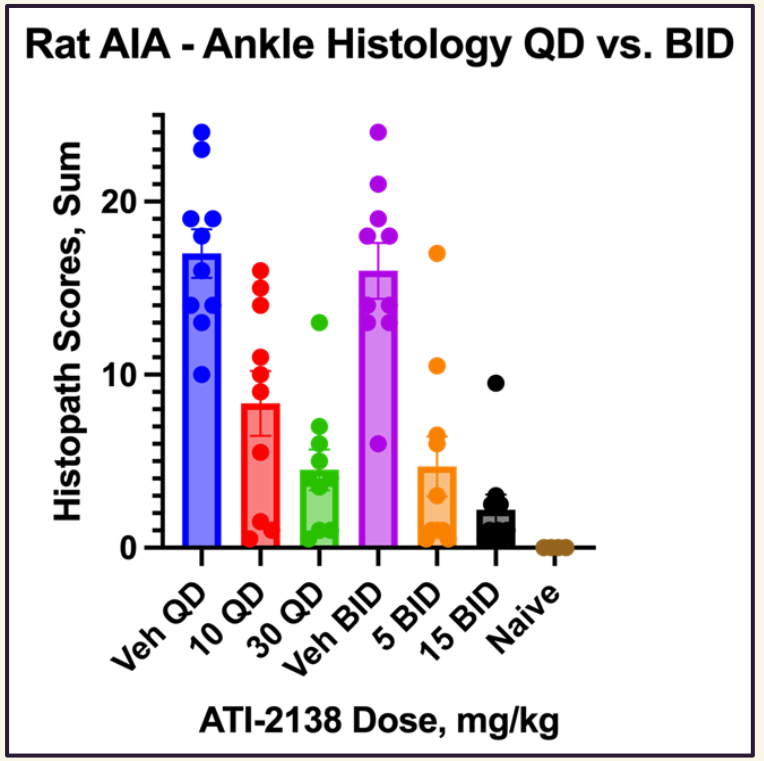


J Sig Trans 2011:DOI:10.1155/2011/297868

ATI-2138 Dose-Dependently Inhibited Adjuvant Induced Arthritis (AIA) in Rats

Ankle Diameter Swelling and Histology



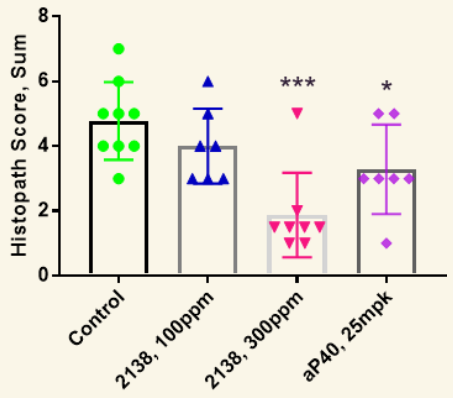


- Semi-therapeutic model with PO dosing beginning on day 6 after FCA injection (Bolder BioPath)[1,2]
- No significant difference between 5 mg/kg BID, 15 mg/kg BID and 30 mg/kg QD

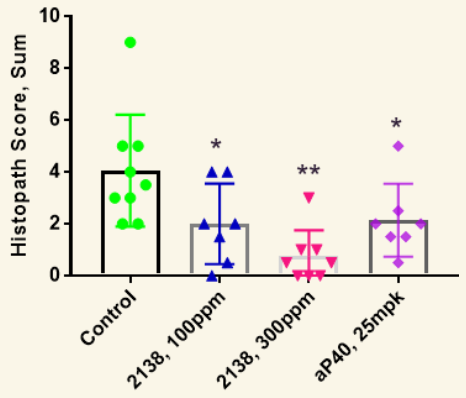
1 Study report RAIA-FCA-CFC-1
2 Data on file

ATI-2138 Dose-Dependently Inhibited Inflammation in the Mouse T Cell Transfer Model of Inflammatory Bowel Disease

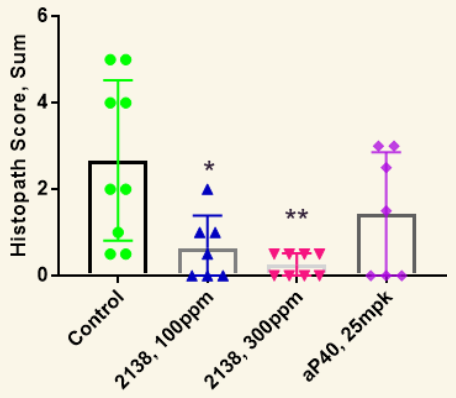
Proximal Colon



Distal Colon



Ileum



ATI-2138 inhibited colitis in the mouse T cell transfer model[1,2,3]

ATI-2138 dose-dependently decreased inflammation in proximal and distal colon, and ileum

Greater effect than anti-IL12 (P40) that significantly decreased inflammation in the proximal and distal colon

1. Study report SR03048; 2. CD4+CD45RB high naïve T cells injected to SCID mice; 3. *p<0.05, **p<0.01, ***p<0.001, vs Control group

ATI-2138 Single (SAD) and Multiple Ascending Dose (MAD) Studies Complete: Data Summary

Safety

- ATI-2138 was generally well tolerated at all doses tested in the trial.
- No serious adverse events were reported.
- The most common adverse events in subjects treated with ATI-2138, and the only events occurring in more than 1 subject, were headache (2 subjects on 5 mg BID, 1 on 40 mg BID, all mild, resolved) and diarrhea (2 subjects on 5 mg BID – both single episodes, both mild).

Pharmacokinetics

- ATI-2138 was rapidly absorbed.
- Multiple doses ranging from 10 to 80 mg daily over two weeks in healthy volunteers showed linear PK and dose-dependent increases in exposure.
- At 10-30 mg daily, ATI-2138 plasma concentration reached the targeted level established using preclinical data.

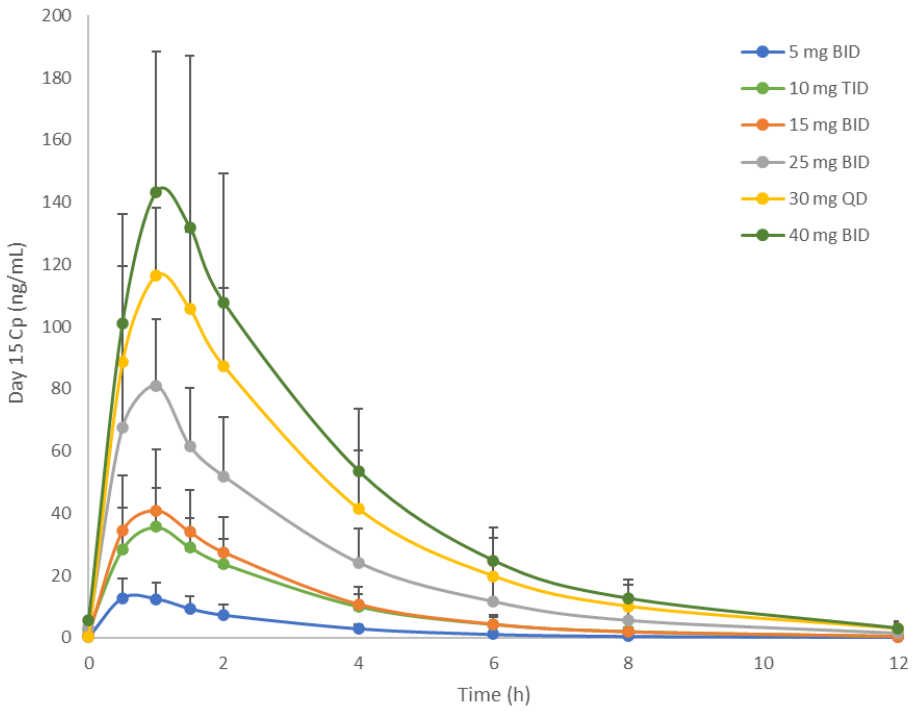
Pharmacodynamics

- Dose-dependent inhibition of both ITK and JAK3 exploratory PD biomarkers was observed.
- 50% to 90% inhibition of the ITK and JAK3 functional markers were observed at 5-15 mg BID, with minimal incremental benefit at higher doses.

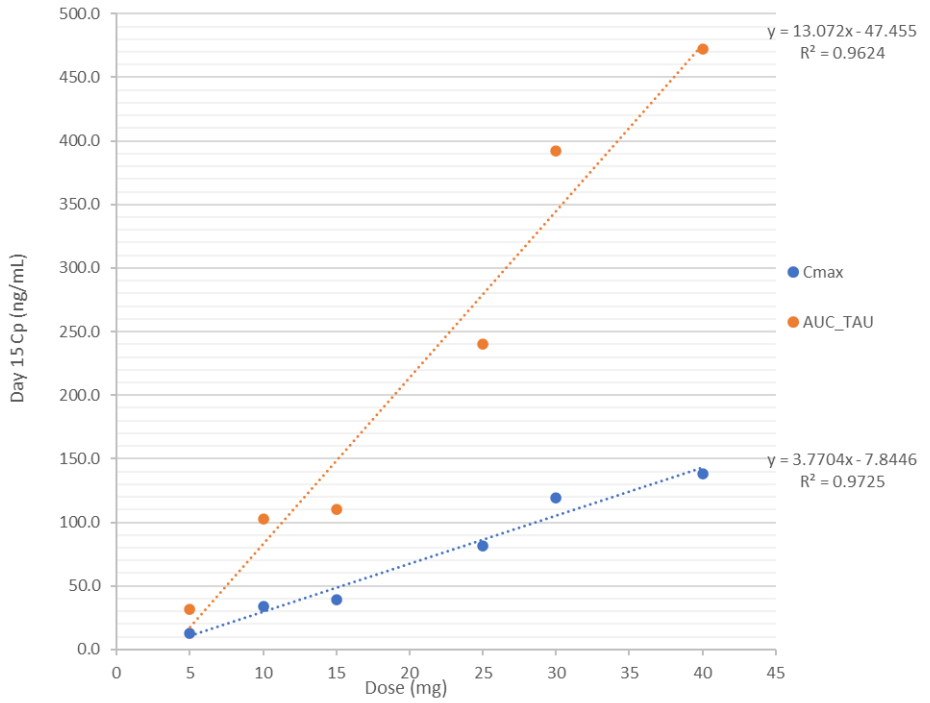
ATI-2138 Pharmacokinetic Analysis from MAD Study

ATI-2138 had linear PK and achieved adequate exposure

ATI-2138 PK



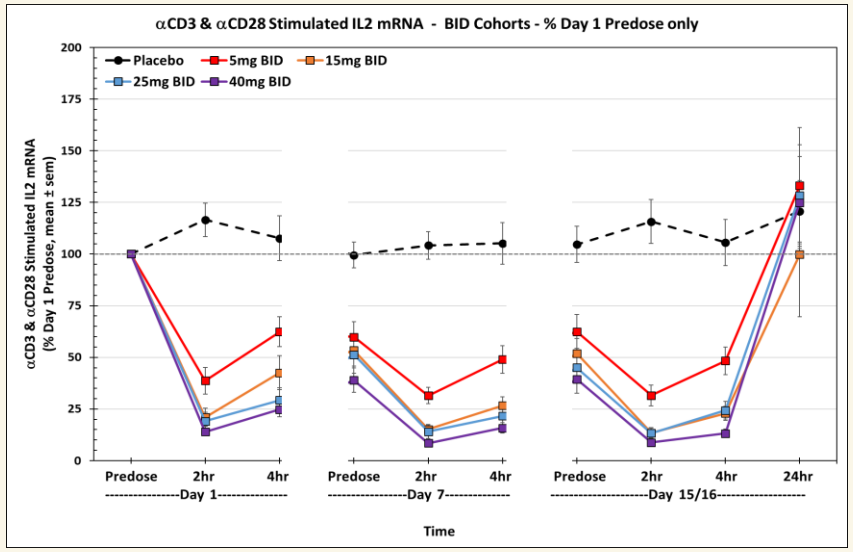
Steady State PK Dose Proportionality

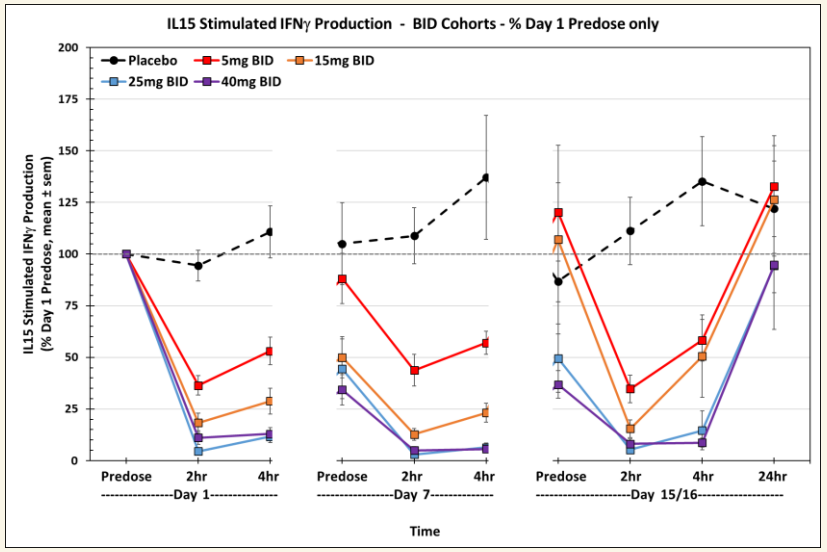


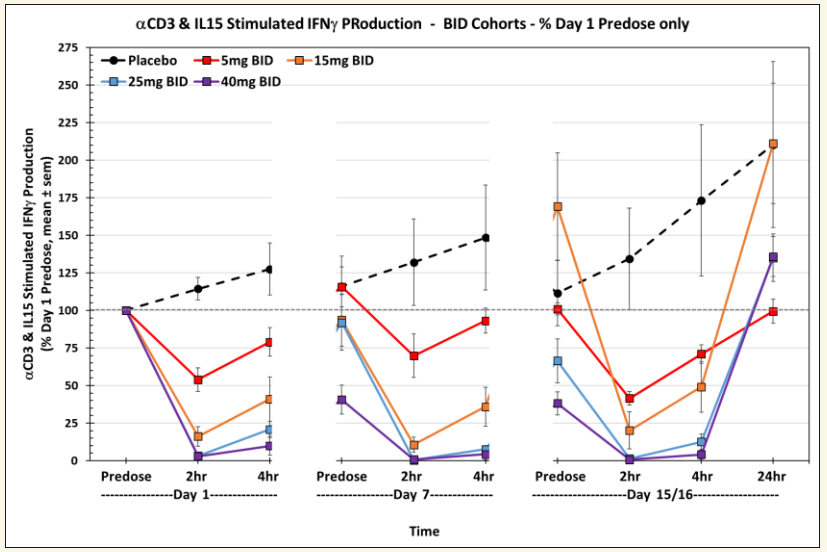
- Day 15 plasma concentration curves demonstrated linear PK for ATI-2138
- Targeted ATI-2138 average exposure over the dosing interval was achieved at doses of 10mg per day and above

ATI-2138 MAD Exploratory Pharmacodynamics

Dose Response Data (BID Cohorts)





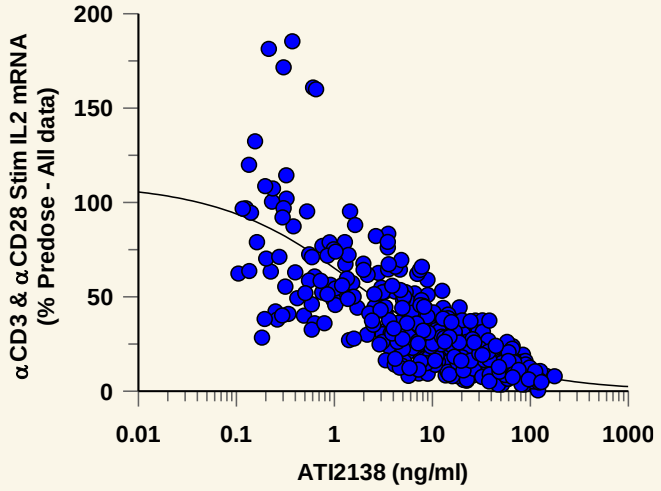


- Pharmacodynamic biomarkers - Ex-vivo stimulation of whole blood taken from subjects before and after administration of ATI-2138 – BID cohorts
- Stimulation with anti-CD3 and anti-CD28 (readout IL-2 mRNA; T-cell activation), IL-15 (readout INFγ; JAK1/3 activation) and dual stimulation (readout INFγ; T-cell and cytokine stimulation)
- ATI-2138 showed dose and time dependent inhibition of all stimulation conditions

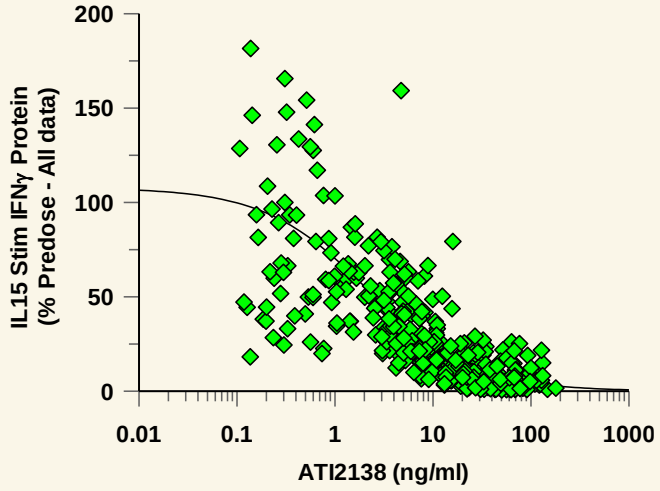
Source – Data on file

High Potency of ATI-2138 for ITK and JAK3 Observed in Preclinical Studies Maintained in the SAD/MAD Clinical Studies

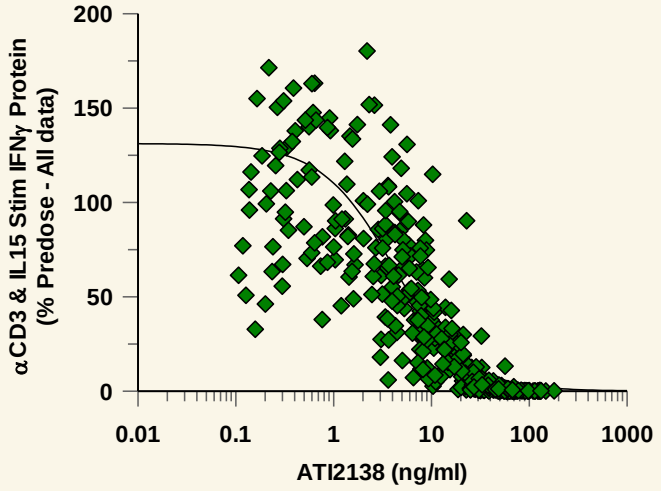
ITK Dependent Response



JAK3 Dependent Response



ITK/JAK3 Response



MAD EC_{50}:	1.9ng/ml / 5.3nM	2.2ng/ml / 6.1nM	4.1ng/ml / 11.4nM
SAD EC_{50}:	5.5ng/ml / 15.2nM	(not evaluated)	2.6ng/ml / 7.3nM
Preclinical IC_{50}*:	7.7ng/ml / 21.3nM	2.9ng/ml / 8.0nM	3.6ng/ml / 10.1nM

- Exposure response data in Phase 1 SAD and MAD clinical studies
- ATI-2138 potency comparison to preclinical cell assay data
- No significant change when comparing Day 1, 7 & 15 EC_{50} values

* Assay configured slightly different from clinical assay

Rationale for Dual Inhibition of ITK and JAK3

ATI-2138 in Atopic Dermatitis

- ITK Inhibition
  - ✓ Atopic dermatitis (AD) is a Th2 cell driven disease and ITK inhibition blocks T cell differentiation/activation and production of IL-4 and IL-13
    - Dupilumab (anti-IL4Rα) and tralokinumab (anti-IL-13) are efficacious in AD
  - ✓ Topical calcineurin inhibitors (TCI; tacrolimus and pimecrolimus) are effective in AD and function downstream of ITK
  - ✓ T cells from AD patients have increased ITK expression[1]
  - ✓ ITK polymorphisms are associated with increased atopy risk[2]
  - ✓ ITK inhibitors are active in murine contact hypersensitivity[3]

- JAK3 Inhibition
  - ✓ JAK3 regulates γ-common cytokines including IL-2 and IL-4
  - ✓ JAK inhibitors (upadacitinib, abrocitinib and baricitinib) are efficacious in AD

1. Matsumoto Y., et al; Identification of Highly Expressed Genes in Peripheral Blood T Cells from Patients with Atopic Dermatitis. *Int Arch Allergy Immunol* 1 December 2002; 129 (4): 327–340; 2. Graves PE, et al. Association of atopy and eczema with polymorphisms in T-cell immunoglobulin domain and mucin domain-IL-2-inducible T-cell kinase gene cluster in chromosome 5 q 33. *J Allergy Clin Immunol*. 2005 Sep;116(3):650-6; 3. von Bonin, A., et al. (2011), Inhibition of the IL-2-inducible tyrosine kinase (Itk) activity: a new concept for the therapy of inflammatory skin diseases. *Experimental Dermatology*, 20: 41-47.

Phase 2a Trial Design of ATI-2138 in Atopic Dermatitis

Eligibility

- Moderate to Severe Atopic Dermatitis
- EASI ≥ 16
- vIGA 3-4
- BSA ≥ 10%
- 18-60 years
- Planned 15 patients

Treatment

- Open label design
- Total 12 weeks treatment
- 10mg BID dosing

Endpoints

- Safety, PK
- PD: RNA analysis, proteomics, IHC to analyze specific pathway inhibition
- EASI-50, -75, -90, % change in EASI
- Change in vIGA, % achieving IGA-TS
- % change BSA, PP-NRS
- POEM, DLQI

ATI-2138: Combined IL-2-Inducible Tyrosine Kinase (ITK) & JAK3 Inhibitor for Autoimmune Disease

- ATI-2138 is an oral compound which interrupts T cell receptor (TCR) signaling by inhibiting ITK and JAK3 signaling of common γ chain cytokines in lymphocytes (including IL-2 & IL-15)
- ATI-2138 potently and selectively inhibits ITK and JAK3 (with some activity at TXK)
- ATI-2138 has demonstrated the prevention of inflammation in animal models of colitis and arthritis
- Safety, pharmacology and toxicology studies have been completed and support further development
- Phase 1 SAD and MAD studies in healthy volunteers have been completed
  - ✓ ATI-2138 was generally well tolerated and no serious adverse events were reported
  - ✓ PK was dose proportional with adequate exposure to block ITK and JAK3 in PD biomarker assays
- Aclaris is evaluating ATI-2138 for the potential treatment of a number of T cell-mediated autoimmune diseases
- A Phase 2a atopic dermatitis trial is in protocol development and operational preparations are under way

The unique pharmacological profile of ATI-2138 provides opportunity for differentiation

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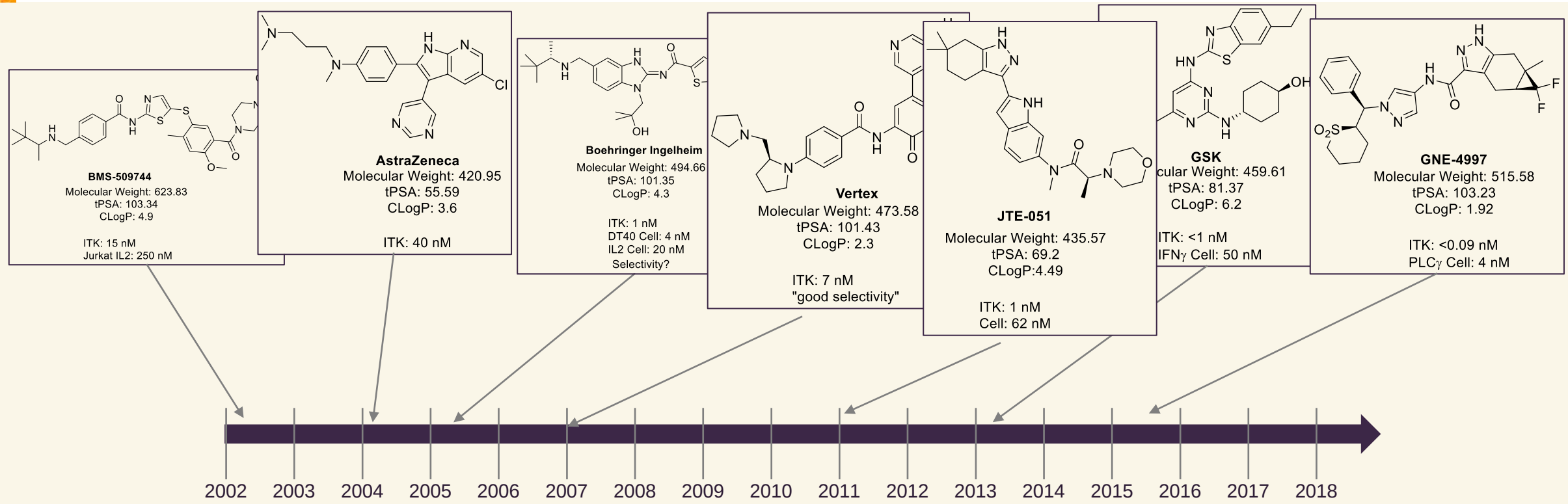
Next Generation Selective ITK Inhibitor

ITK is an Interesting but Hard to Drug Target

Reversible ATP competitive inhibitors discontinued for weak cellular potency, poor ADME



- Compounds targeting the ATP site of ITK have been pursued since the early 2000's across Pharma
  - ✓ Only JTE-051 reached development and was discontinued
- Covalent ITK inhibitors
  - ✓ CPI-818 is in clinical trials for T cell lymphoma and AD

Charrier, J-D, Knegtel, R. MA. (2013): Advances in the design of ITK inhibitors. Expert Opin. Drug Disc. 8(4):369-381

Burch, D. J., et al. (2015): Tetrahydroindazoles as Interleukin-2 Inducible T-Cell Kinase Inhibitors. Part II. Second-Generation Analogues with Enhanced Potency, Selectivity, and Pharmacodynamic Modulation in Vivo, J. Med. Chem. 58: 3806-3816.

Alder, C. M. (2013): Identification of a Novel and Selective Series of Itk Inhibitors via a Template-Hopping Strategy, Med. Chem. Lett. 4(10) 948-952.

ITK Selective Covalent Inhibitor

Next Generation Follow-on to ATI-2138

- ATI-2138 is a dual pathway inhibitor of ITK and JAK3 mediated cytokine signaling pathways
- Goal of next generation inhibitor is to minimize crossover onto JAK3
- Selective targeting of ITK (T_H2 and T_H17 inhibition) and/or ITK/TXK (broad T cell inhibition) while sparing JAK3 should result in more specific T cell modulating drugs

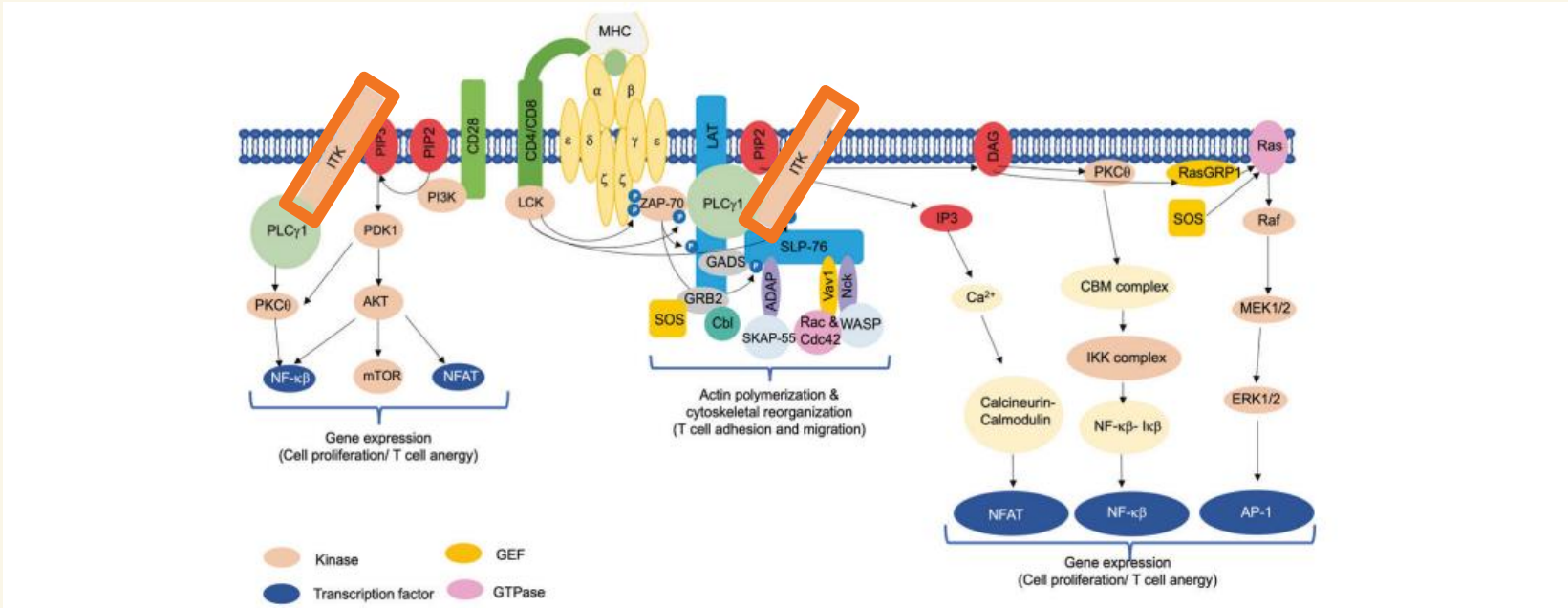
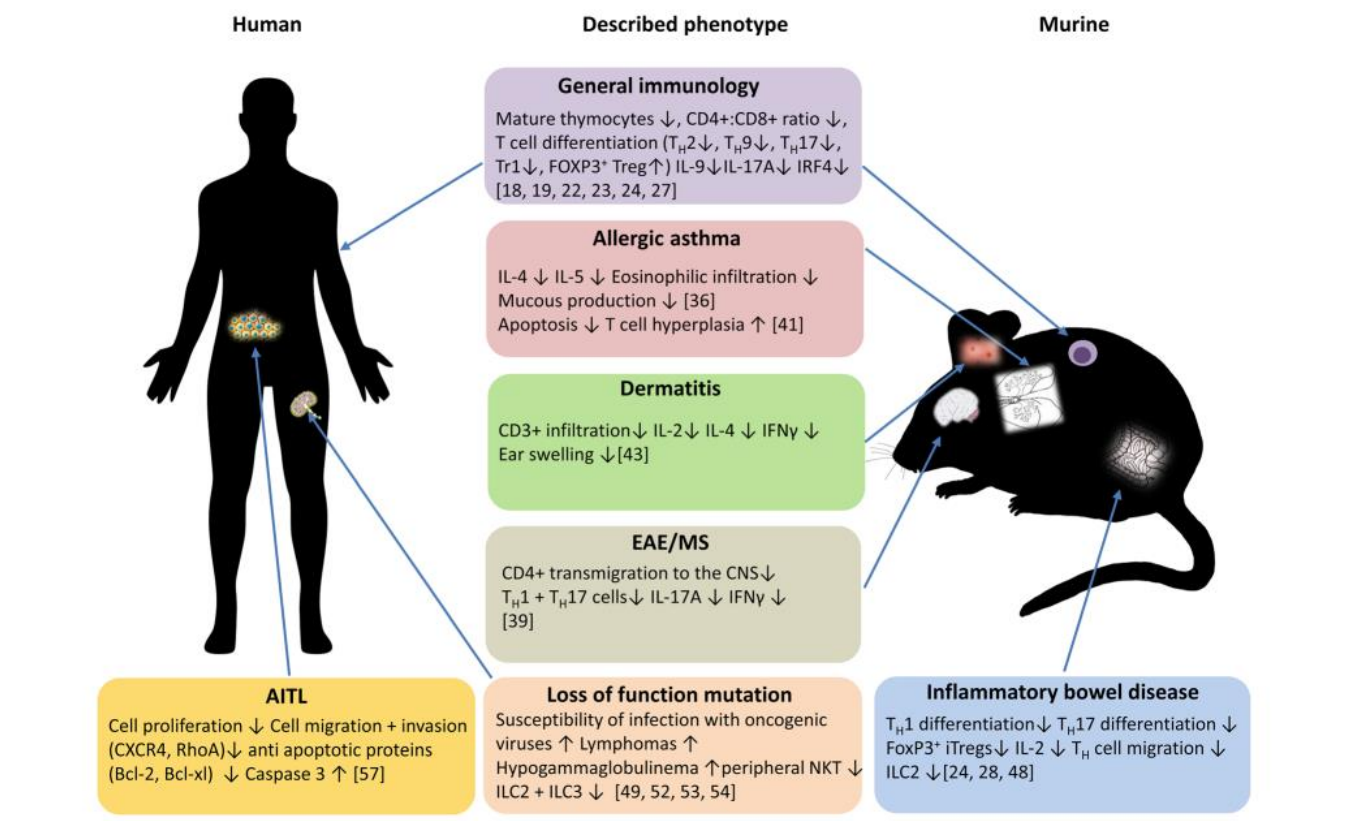


Fig. 3 Positive regulation of T cell signaling. The figure depicts the activation of various enzymes and adaptor molecules upon engagement of TCR with the MHC antigenic peptide complex. The phosphorylation events carried out are depicted as small, blue-colored circles. Black lines with arrows indicate activation.

Shah K, et al. (2021) T cell receptor (TCR) signaling in health and disease. Signal Transduct Target Ther. 13;6(1):412

ITK Selective Inhibitor: Potential Indications

Multiple potential indications supported by ITK genetic phenotypes
RA, AD, cGVHD, solid organ transplant rejection, MS, IBD



Lechner, K. S. et al. (2020) Role of the IL-2 Inducible tyrosine kinase ITK and its inhibitors in disease pathogenesis. J. Mol. Medicine 98:1385-1395
Weeks S et al. (2021) Targeting ITK signaling for T cell-mediated diseases. iScience. 24(8):102842.

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