UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d) of
The Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): May 7, 2024

Aclaris Therapeutics, Inc.
(Exact name of registrant as specified in its charter)

Delaware	**001-37581**	**46-0571712**
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification No.)

701 Lee Road, Suite 103
Wayne, PA 19087
(Address of principal executive offices, including zip code)

(484) 324-7933
(Registrant's telephone number, including area code)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class:	Trading Symbol(s)	Name of Each Exchange on which Registered
Common Stock, $0.00001 par value	ACRS	The Nasdaq Stock Market, LLC

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 2.02 Results of Operations and Financial Condition.

On May 7, 2024, Aclaris Therapeutics, Inc. (the "***Registrant***") issued a press release announcing its financial results for the quarter ended March 31, 2024, as well as information regarding a conference call to discuss business updates. A copy of this press release is furnished herewith as Exhibit 99.1 to this Current Report.

In accordance with General Instruction B.2. of Form 8-K, the information in this Item 2.02 and Exhibit 99.1 hereto shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "***Exchange Act***"), or otherwise subject to the liability of that section, nor shall it be deemed incorporated by reference in any of the Registrant's filings under the Securities Act of 1933, as amended (the "***Securities Act***"), or the Exchange Act, whether made before or after the date hereof, regardless of any incorporation language in such a filing, except as expressly set forth by specific reference in such a filing.

Item 7.01 Regulation FD Disclosure.

On May 7, 2024, the Registrant will hold a conference call to provide a corporate update. The conference call will include a slide presentation. A copy of the slide presentation that will accompany the conference call is furnished as Exhibit 99.2 to this Current Report.

In accordance with General Instruction B.2. of Form 8-K, the information in this Item 7.01 and Exhibit 99.2 hereto shall not be deemed "filed" for purposes of Section 18 of the Exchange Act or otherwise subject to the liability of that section, nor shall it be deemed incorporated by reference in any of the Registrant's filings under the Securities Act or the Exchange Act, whether made before or after the date hereof, regardless of any incorporation language in such a filing, except as expressly set forth by specific reference in such a filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit Number	Exhibit Description
99.1	Press Release, dated May 7, 2024.
99.2	Company Presentation.
104	The cover page from Aclaris Therapeutics, Inc.'s Form 8-K filed on May 7, 2024, formatted in Inline XBRL.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

ACLARIS THERAPEUTICS, INC.

Date: May 7, 2024

By: /s/ Kevin Balthaser
Kevin Balthaser
Chief Financial Officer

Aclaris Therapeutics Reports First Quarter 2024 Financial Results and Provides a Corporate Update

- Progressing ATI-2138 into Atopic Dermatitis -
- Management to Host Conference Call at 5:00 PM ET Today -

WAYNE, Pa., May 07, 2024 (GLOBE NEWSWIRE) -- Aclaris Therapeutics, Inc. (NASDAQ: ACRS), a clinical-stage biopharmaceutical company focused on developing novel drug candidates for immuno-inflammatory diseases, today announced its financial results for the first quarter of 2024 and provided a corporate update.

"We are pleased to announce that following a review of the potential development pathways for ATI-2138, our investigational ITK/JAK3 compound with best-in-class potential, we have decided to progress ATI-2138 into a proof-of-concept Phase 2a trial in patients with moderate to severe atopic dermatitis," stated Dr. Neal Walker, co-founder and Interim Chief Executive Officer & President of Aclaris. "Across all of our programs, we remain focused on executing a capital efficient strategy to advance novel immuno-inflammatory therapies."

Research and Development Highlights:

- **ITK Inhibitor Programs**
  - **ATI-2138**, an investigational oral covalent ITK/JAK3 inhibitor
    - Aclaris plans to progress ATI-2138 into a Phase 2a trial in subjects with moderate to severe atopic dermatitis.
    - In September 2023, Aclaris reported positive results from its Phase 1 multiple ascending dose (MAD) trial of ATI-2138.
  - **ITK Selective Compound**
    - Aclaris is progressing to development candidate selection a second generation ITK selective inhibitor for autoimmune indications.
- **Lepzacitinib (ATI-1777)**, an investigational topical "soft" JAK 1/3 inhibitor
  - In January 2024, Aclaris reported positive top-line results from its Phase 2b trial in atopic dermatitis (AD).
  - Aclaris is currently seeking a global development and commercialization partner for this program (excluding Greater China). As previously announced, in 2022 Aclaris granted Pediatrix Therapeutics exclusive rights to develop and commercialize lepzacitinib in Greater China.
- **Zunsemetinib (ATI-450)**, an investigational oral small molecule MK2 inhibitor
  - Aclaris plans to support Washington University in St. Louis in its investigator-initiated Phase 1b/2 trials of zunsemetinib as a potential treatment for pancreatic cancer and metastatic breast cancer. Aclaris expects these trials to be primarily funded by grants awarded to Washington University.

Financial Highlights:

Liquidity and Capital Resources

As of March 31, 2024, Aclaris had aggregate cash, cash equivalents and marketable securities of $161.4 million compared to $181.9 million as of December 31, 2023. A majority of cash expenditures in the first quarter of 2024 were related to payments associated with exit activities, including the wind down of discontinued R&D programs and the previously announced reduction in force. Aclaris anticipates payments associated with these activities to be substantially completed by the second quarter of 2024. As a result, Aclaris expects significantly lower quarterly cash expenditures in future quarters, without giving effect to any potential business development activities resulting from its ongoing strategic review of its business.

Financial Results

First Quarter 2024

- Net loss was $16.9 million for the first quarter of 2024 compared to $28.2 million for the first quarter of 2023.
- Total revenue was $2.4 million for the first quarter of 2024 compared to $2.5 million for the first quarter of 2023. The decrease was primarily driven by lower contract research revenue during the three months ended March 31, 2024.
- Research and development (R&D) expenses were $9.8 million for the quarter ended March 31, 2024 compared to $22.6 million for the prior year period.
    - The $12.8 million decrease was primarily the result of lower:
        - Zunsemetinib development expenses associated with clinical activities for a Phase 2a trial for hidradenitis suppurativa, a Phase 2b trial for rheumatoid arthritis, and drug candidate manufacturing costs.
        - Costs associated with lepzacitinib preclinical development activities and a Phase 2b clinical trial for AD.
        - ATI-2138 development expenses, including costs associated with a Phase 1 MAD trial and other preclinical activities.
        - Compensation-related expenses due to a decrease in headcount and higher forfeiture credits.
- General and administrative (G&A) expenses were $6.8 million for the quarter ended March 31, 2024 compared to $8.8 million for the prior year period. The decrease was primarily due to a reduction in compensation-related expenses due to lower headcount and higher forfeiture credits.
- Licensing expenses were $1.0 million for the quarter ended March 31, 2024 compared to $1.1 million for the prior year period. The decrease was due to the achievement of a commercial milestone during the three months ended March 31, 2023, offset by an increase in royalties earned under the Lilly license agreement.
- Revaluation of contingent consideration resulted in a $2.8 million loss for the quarter ended March 31, 2024 compared to a gain of $0.8 million for the prior year period.

Conference Call and Webcast

As previously disclosed on April 30, 2024, management will host a conference call and webcast, with an accompanying slide presentation, at 5:00 PM ET today to provide a corporate update. To access the live webcast of the call and the accompanying slide presentation, please visit the “Events” page of the “Investors” section of Aclaris’ website, www.aclaristx.com. The webcast will be archived for at least 30 days on the Aclaris website.

About Aclaris Therapeutics, Inc.

Aclaris Therapeutics, Inc. is a clinical-stage biopharmaceutical company developing a pipeline of novel drug candidates to address the needs of patients with immuno-inflammatory diseases who lack satisfactory treatment options. The company has a multi-stage portfolio of drug candidates powered by a robust R&D engine exploring protein kinase regulation. For additional information, please visit www.aclaristx.com.

Cautionary Note Regarding Forward-Looking Statements

Any statements contained in this press release 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 its plans for its development programs, including its plans to seek a development and commercialization partner for lepzacitinib, the clinical development of ATI-2138, and its plan to support Washington University in St. Louis in its investigator-initiated Phase 1b/2 trials of zunsemetinib, as well as Aclaris’ expectations regarding the wind down of discontinued R&D programs and costs associated with its recent reduction in force and the associated impact on anticipated cash burn, and its strategic review of its business. 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 press release and are based on information available to Aclaris as of the date of this release, 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.

Aclaris Therapeutics, Inc.
Condensed Consolidated Statements of Operations
(unaudited, in thousands, except share and per share data)

	Three Months Ended March 31,	
	2024	2023
Revenues:		
Contract research	$ 657	$ 889
Licensing	1,741	1,639
Total revenue	2,398	2,528
Costs and expenses:		
Cost of revenue [1]	809	808
Research and development [1]	9,845	22,587
General and administrative [1]	6,844	8,790
Licensing	1,031	1,061
Revaluation of contingent consideration	2,800	(800)
Total costs and expenses	21,329	32,446
Loss from operations	(18,931)	(29,918)
Other income, net	1,990	1,758
Net loss	$ (16,941)	$ (28,160)
Net loss per share, basic and diluted	$ (0.24)	$ (0.42)
Weighted average common shares outstanding, basic and diluted	71,074,858	66,872,778
(1) *Amounts include stock-based compensation expense as follows:*		
Cost of revenue	$ 252	$ 299
Research and development	(29)	2,602
General and administrative	1,866	3,905
Total stock-based compensation expense	$ 2,089	$ 6,806

Aclaris Therapeutics, Inc.
Selected Consolidated Balance Sheet Data
(unaudited, in thousands, except share data)

	March 31, 2024	December 31, 2023
Cash, cash equivalents and marketable securities	$ 161,365	$ 181,877
Total assets	$ 174,065	$ 197,405
Total current liabilities	$ 20,080	$ 30,952
Total liabilities	$ 32,051	$ 40,226
Total stockholders' equity	$ 142,014	$ 157,179
Common stock outstanding	71,248,017	70,894,889

Aclaris Therapeutics, Inc.
Selected Consolidated Cash Flow Data
(unaudited, in thousands)

	March 31, 2024	March 31, 2023
Net loss	$ (16,941)	$ (28,160)
Depreciation and amortization	243	198
Stock-based compensation expense	2,089	6,806
Revaluation of contingent consideration	2,800	(800)
Changes in operating assets and liabilities	(9,006)	(4,397)
Net cash used in operating activities	$ (20,815)	$ (26,353)

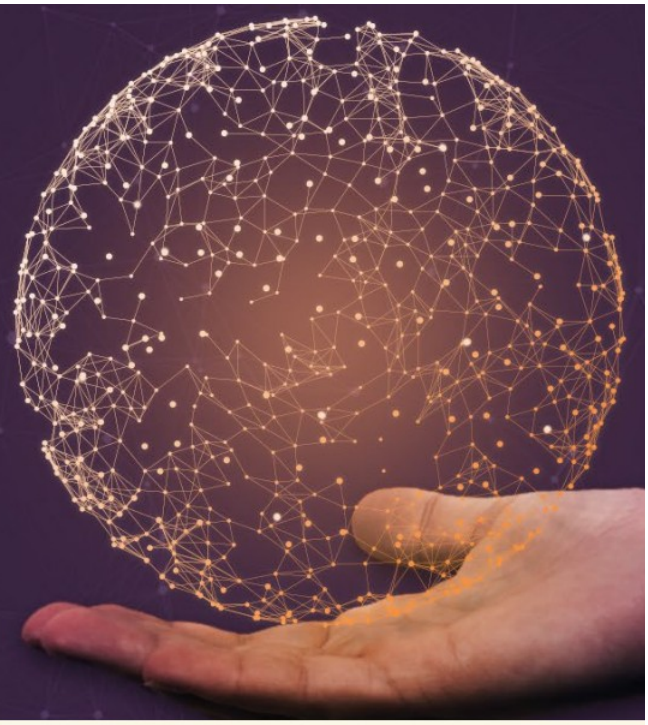
Aclaris Therapeutics Contact:

investors@aclaristx.com

EMPOWERING PATIENTS THROUGH KINOME INNOVATION

Overview of ITK Portfolio

May 7, 2024



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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.

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

(Investigational Drug Candidate)

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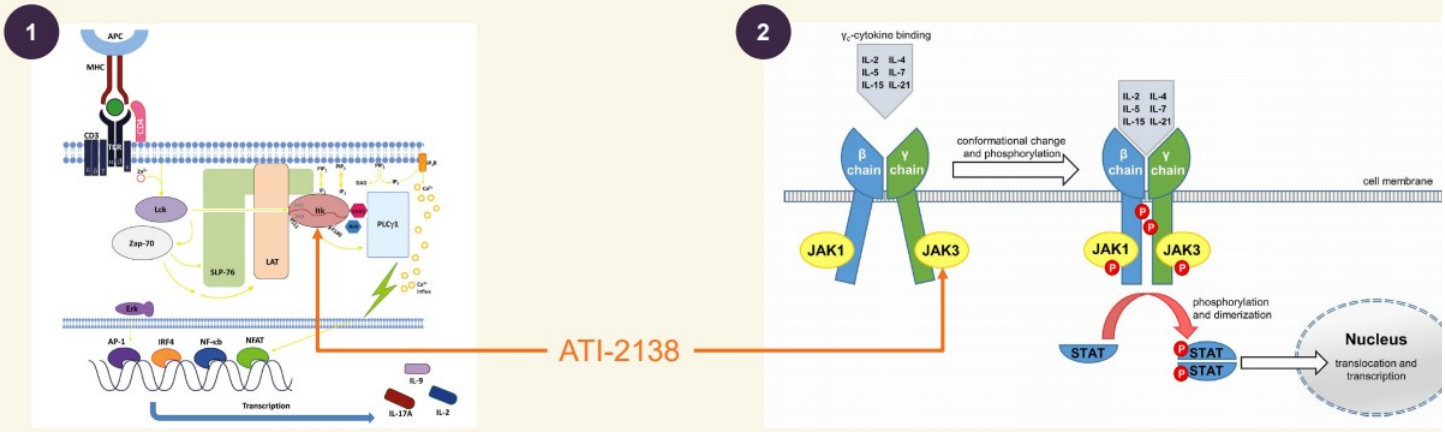
ATI-2138 is a Combined Covalent IL-2-Inducible Tyrosine Kinase (ITK) & JAK3 Inhibitor for Autoimmune Disease



- 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, Gehringe 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

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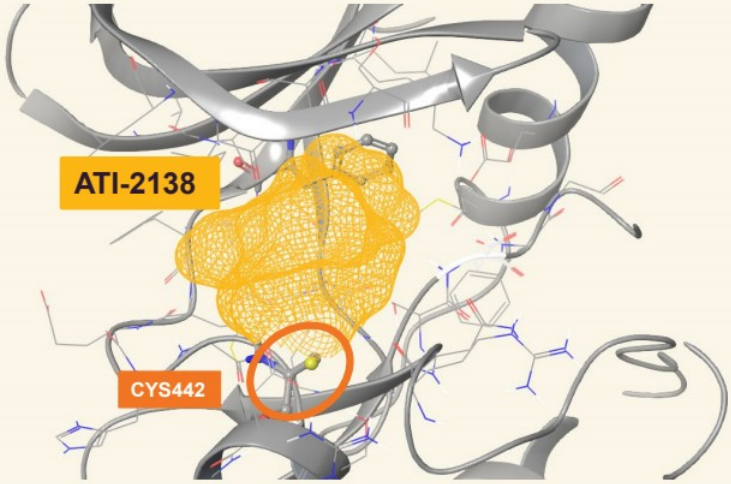
ATI-2138 Covalently Inhibits ITK and JAK3

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



- 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)

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ATI-2138: Potential for Meaningful Differentiation

ATI-2138, by modulating both TCR signaling (via ITK blockade) and cytokine signaling (via JAK3 blockade), is
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

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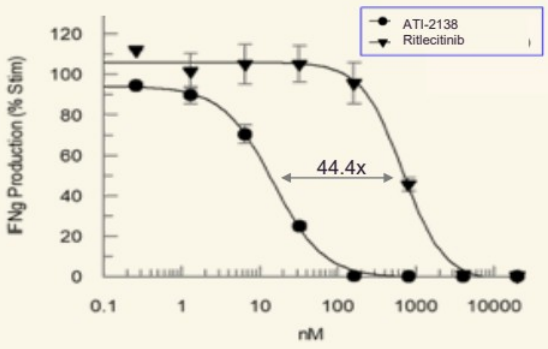
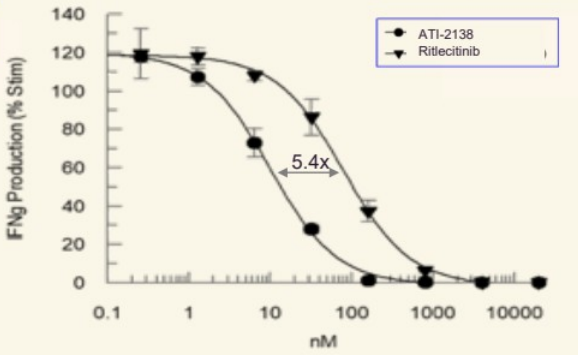
ATI-2138 Differentiation from Ritlecitinib

Dual ITK and JAK3 Inhibitors

ITK: HWB αCD3 Stimulated IFNγ Release



JAK3: HWB IL2 Stimulated IFNγ Release

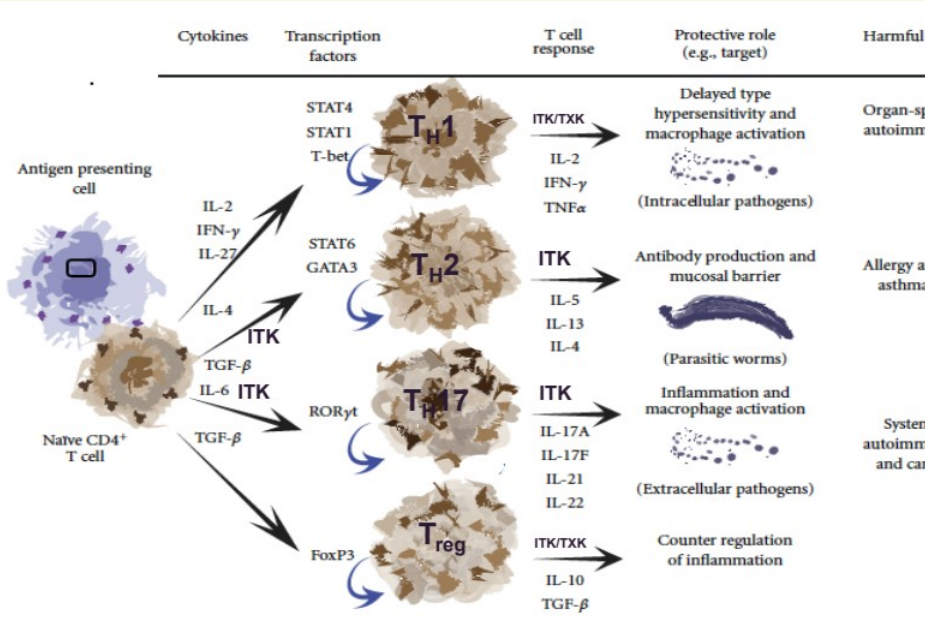


- ATI-2138 is 44.4x more potent than ritlecitinib for inhibiting αCD3 induced IFNγ production (ITK) and 5.4x more potent for inhibiting JAK3 dependent IL-2 induced IFNγ production in human whole blood
- At the FDA recommended 50 mg QD dose for alopecia areata, ritlecitinib plasma levels may not impact 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

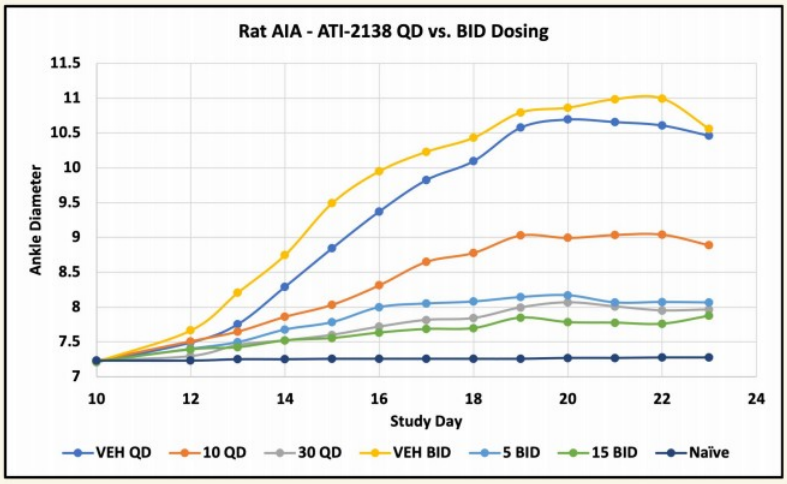
- ITK has a nonredundant role in the differentiation and activation of T_H2 and T_H17 cells
- Knockdown or inhibition of ITK in mice and humans results in skewing of T helper cells from T_H2 and T_H17 toward T_H1 and T_{reg}
- Blockade of T_H2 function inhibits production of IL-4 and IL-13, two cytokines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

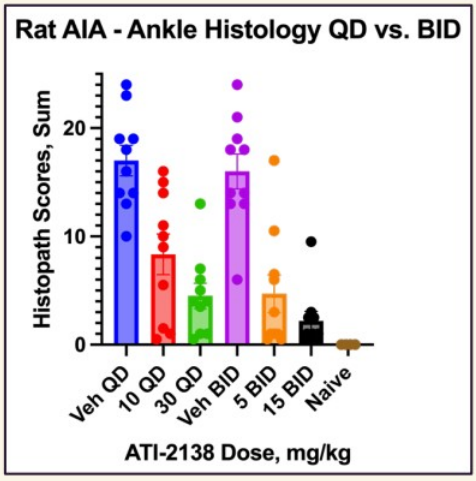


J Sig Trans 2011:DOI:10.1155/2011/297868

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

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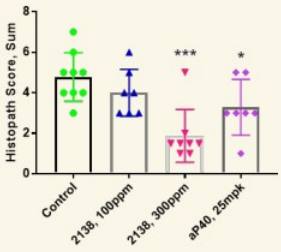
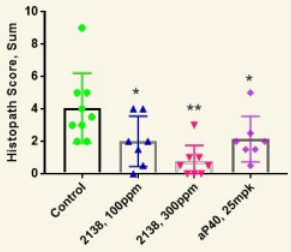
ATI-2138 Dose-Dependently Inhibited Inflammation in the Mouse T Cell Transfer Model of Inflammatory Bowel Disease

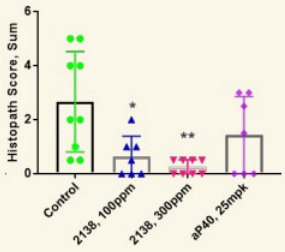
Proximal Colon



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

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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.

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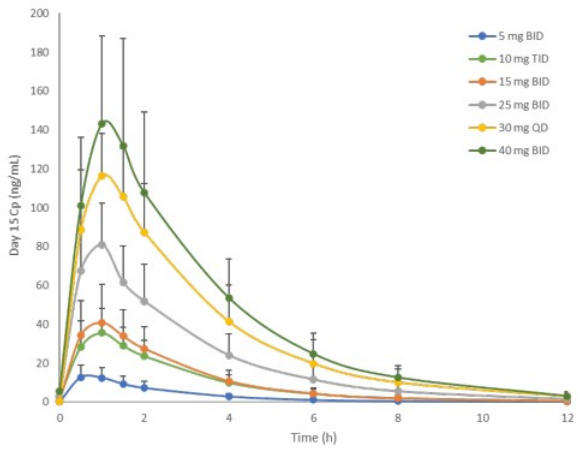
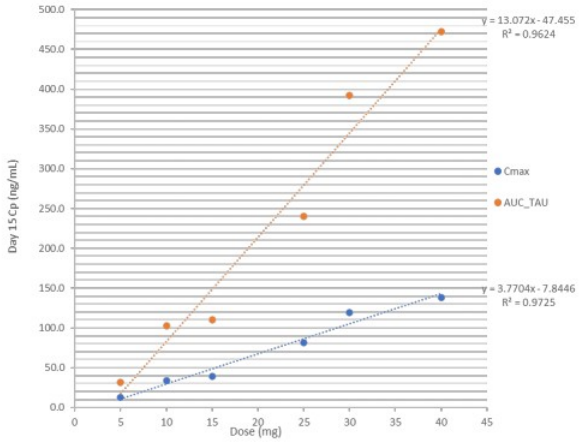
ATI-2138 Pharmacokinetic Analysis from MAD Study

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

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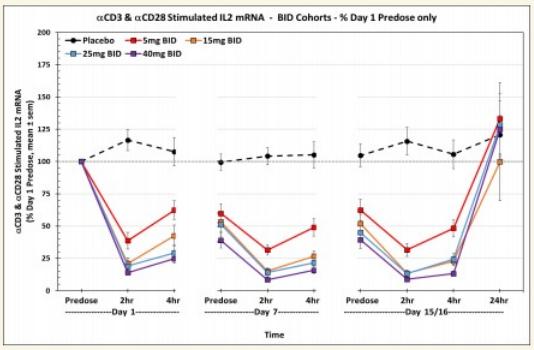
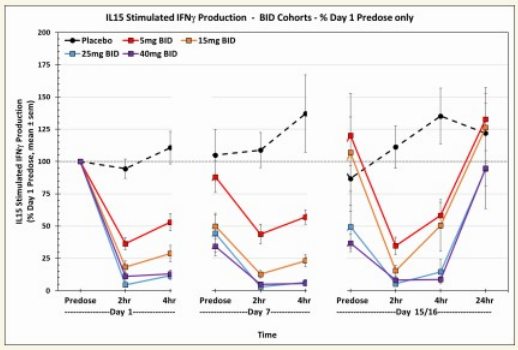
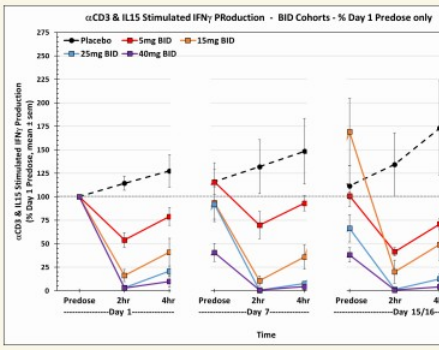
ATI-2138 MAD Exploratory Pharmacodynamics

Dose Response Data (BID Cohorts)



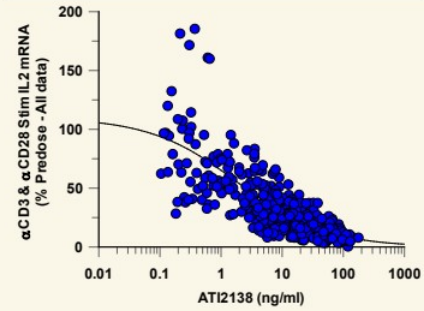
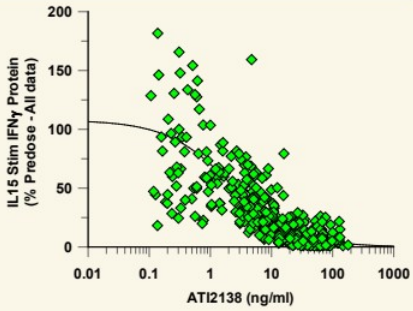
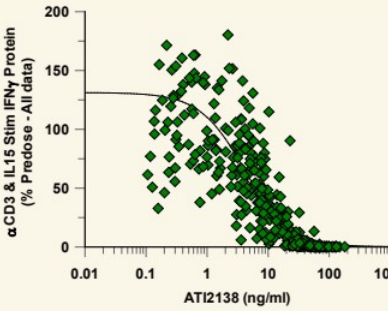




- Pharmacodynamic biomarkers - Ex-vivo stimulation of whole blood taken from subjects before and after administration of ATI-2138 – BID cohorts
- Stimulation with anti-CD3 and anti-CD28 (readout IL-2 mRNA; T-cell activation), IL-15 (readout INFγ; JAK1/3 activation) and dual stimulation (readout INFγ;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

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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.

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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

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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

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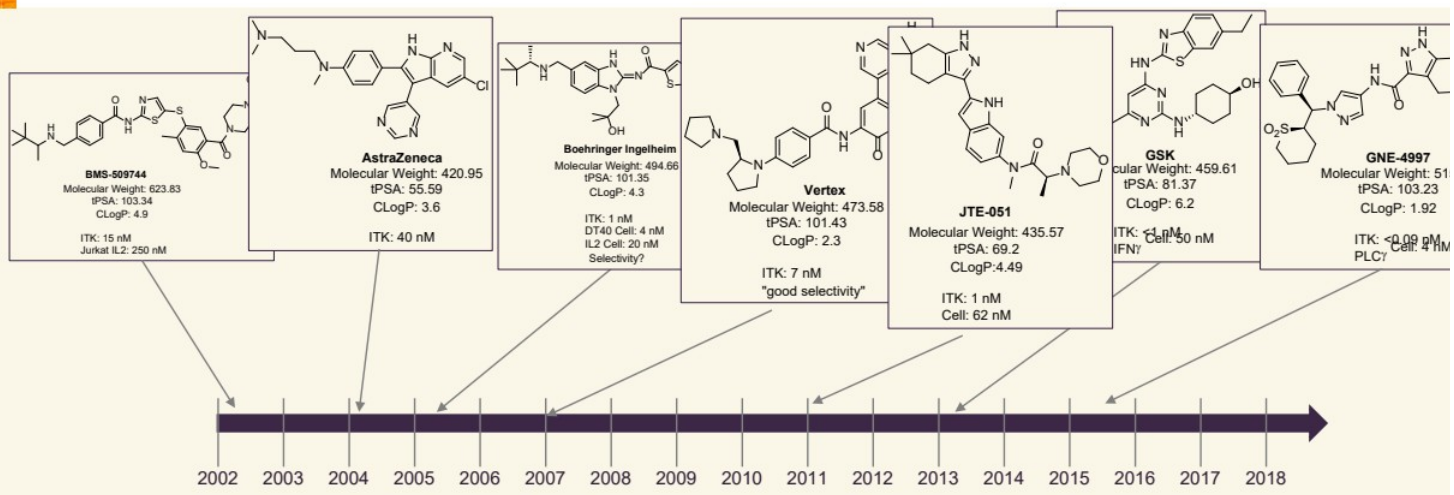
ITK is an Interesting but Hard to Drug Target

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.

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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

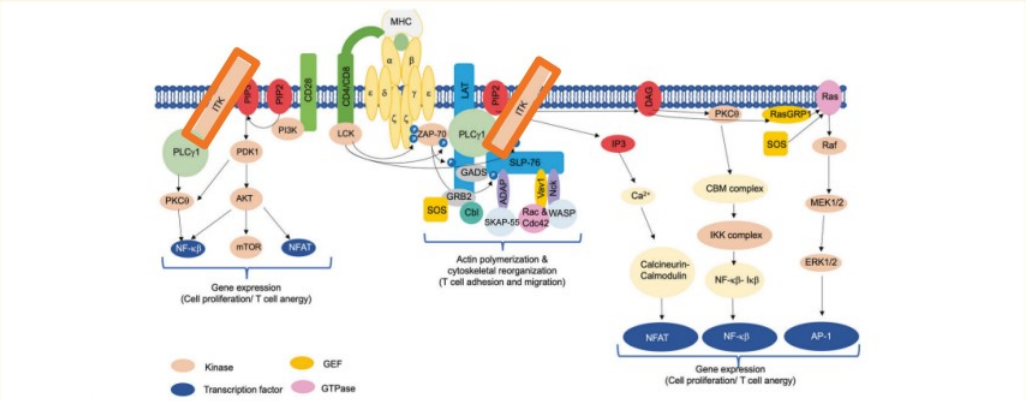

Fig. 3 Positive regulation of T cell signaling. The figure depicts the activation of various enzymes and adaptor molecules upon engagement of TCR with the MHC antigenic peptide complex. The phosphorylation events carried out are depicted as small, blue-colored circles. Black lines with arrows indicate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

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

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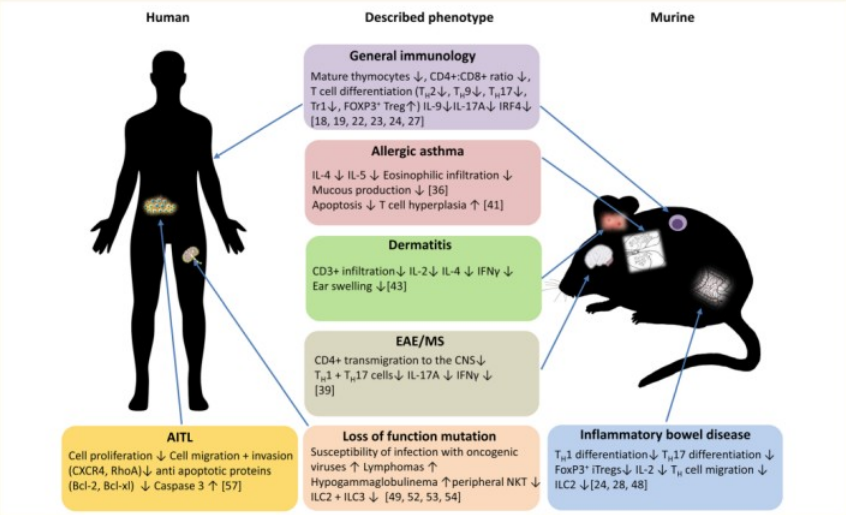
ITK Selective Inhibitor: Potential Indications

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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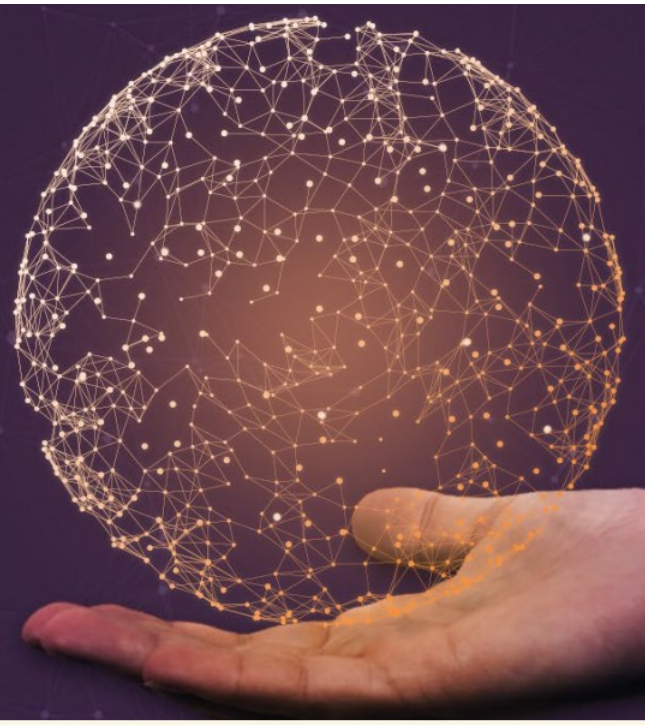
EMPOWERING PATIENTS THROUGH KINOME INNOVATION

Overview of ITK Portfolio

May 7, 2024



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