EMPOWERING PATIENTS THROUGH
KINOME INNOVATION

Aclaris Therapeutics Virtual R&D Day

The Productivity of the Platform

December 7, 2021

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Cautionary Note Regarding Forward-Looking Statements

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 “believe,” “expect,” “may,” “plan,” “potential,” “will,” and similar expressions, and are based on Aclaris' current beliefs and expectations. These forward-looking statements include expectations regarding Aclaris’ development of its drug candidates, including the timing of its clinical trials and regulatory submissions. 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, **the uncertainty regarding the COVID-19 pandemic including its impact on the timing of Aclaris’ regulatory and research and development activities**, 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, 2020 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 http://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.

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Agenda & Presenters

- Introduction
  - ✓ Portfolio Overview
- MK2 Inhibitor Program
  - ✓ Clinical Update on Zunsemetinib (ATI-450), an Investigational MK2 Inhibitor
  - ✓ Role of MK2 in IL-17 Biology
  - ✓ ATI-2231: An Investigational MK2 Inhibitor for Oncology
- ATI-2138, an Investigational ITK/TXK/JAK3 Inhibitor
- Oral Gut-Biased JAK Inhibitors for Inflammatory Bowel Disease
- Closing Remarks and Q&A Session

- Co-founded Aclaris in 2012
- Board-certified dermatologist
- Serial entrepreneur with over 20 years of experience in the life sciences industry

Neal Walker

Co-founder, President & CEO, Director

- Former Executive Director, Pfizer Inflammation Research and Leader of Global Kinase Technology Team
- >95 publications and patents (>30 total on kinases)

Joseph Monahan, PhD

Chief Scientific Officer

- Immunologist/drug discovery leader at pharma (Pfizer & biotech)
- Validated JAK 1/3 as target for transplant/RA/psoriasis, leading to approval of XELJANZ®

Paul Changelian, PhD

VP, Biology

Portfolio Overview

Biopharmaceutical Company Focused on the Kinome:
People + Platform + Pipeline

LEADERSHIP

Founded and Led by Physicians and Scientists

- World class ex-Pfizer (kinase) and ex-GSK (immunology) leadership
- Kinome experts skilled at developing kinase targeted medicines

KINect® PLATFORM

Proprietary Kinase Discovery Engine

- Versatile platform
- Fully integrated discovery and development team
- Advancing small molecule drug candidates designed to parallel or exceed efficacy of high-value biologics

INNOVATIVE PIPELINE
(investigational drug candidates)

Zunsemetinib (ATI-450) - MK2i

- Oral anti-TNFα, anti-IL1, anti-IL6

ATI-1777 - Topical "Soft" JAK1/3i

- Tissue specific therapy for the potential treatment of moderate to severe atopic dermatitis (AD)

ATI-2138 - ITK/TXK/JAK3i

- Oral dual inhibitor of T-cell and cytokine receptors

Development of Small Molecule Therapeutics for Immuno-inflammatory Diseases

KINect® is a registered trademark of Aclaris Therapeutics, Inc.

Drug Development Pipeline

Drug Candidate / Program	Target	Route of Administration	Indication	Development Phase
Immuno-Inflammatory Diseases				
Zunsemetinib (ATI-450)	MK2 inhibitor	Oral	Rheumatoid arthritis (moderate to severe)	Phase 2
			Hidradenitis suppurativa (moderate to severe)	Phase 2*
			Psoriatic arthritis (moderate to severe)	Phase 2*
ATI-1777	"Soft" JAK 1/3 inhibitor	Topical	Atopic dermatitis (moderate to severe)	Phase 2
ATI-2138	ITK/TXK/JAK3 inhibitor	Oral	Psoriasis	IND Allowed
Gut-Biased Program	JAK inhibitor	Oral	Inflammatory bowel disease	Discovery
Oncology				
ATI-2231	MK2 inhibitor	Oral	Metastatic breast cancer	Preclinical
			Pancreatic cancer	

* We plan to progress these indications directly into Phase 2

MK2 Inhibitor Program:

- Clinical Update on Zunsemetinib (ATI-450), an Investigational MK2 Inhibitor

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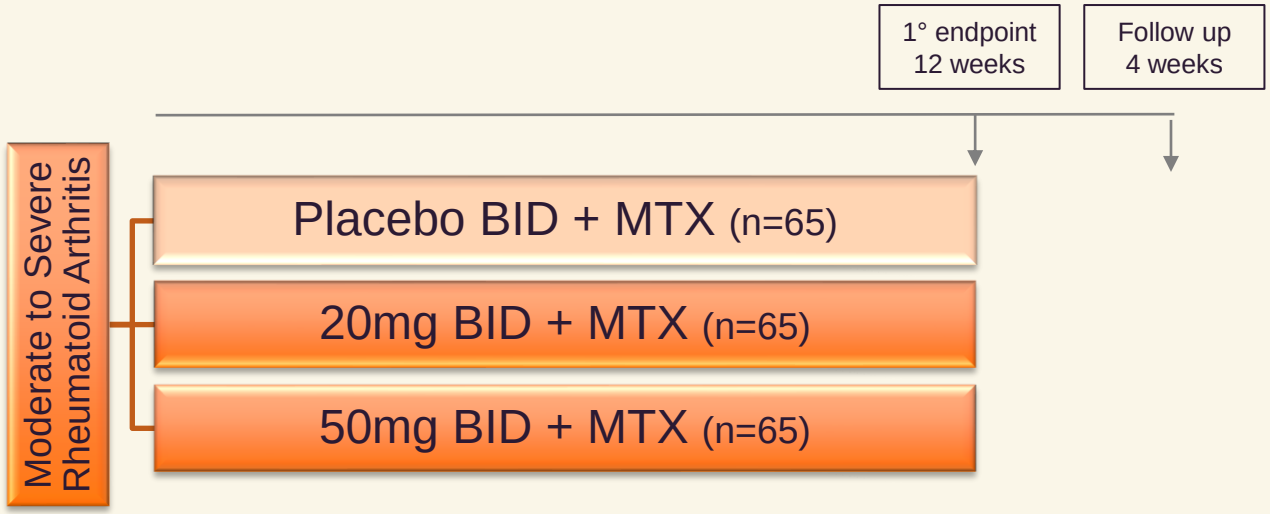
Zunsemetinib (ATI-450) Clinical Studies (1)

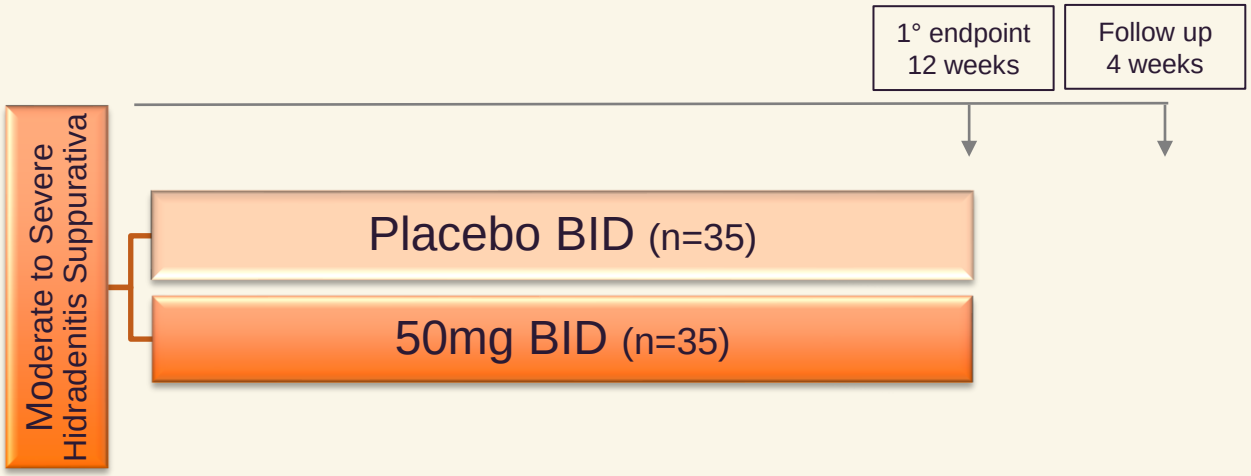
ATI-450-RA-202: Adult methotrexate inadequate responders



Primary Endpoint
- ACR 20 responders

Secondary Endpoints Include:
- ACR 50, 70
- DAS-28 change/remission
- CDAI
- Safety
- PK + PD

ATI-450-HS-201: Adults with inflammatory abscess and/or nodule (AN) count of ≥5



Primary Endpoint
- Change inflammatory nodule/abscess count

Secondary Endpoints Include:
- HiSCR, IHS4, Hurley
- Pain, DLQI
- Safety
- PK + PD

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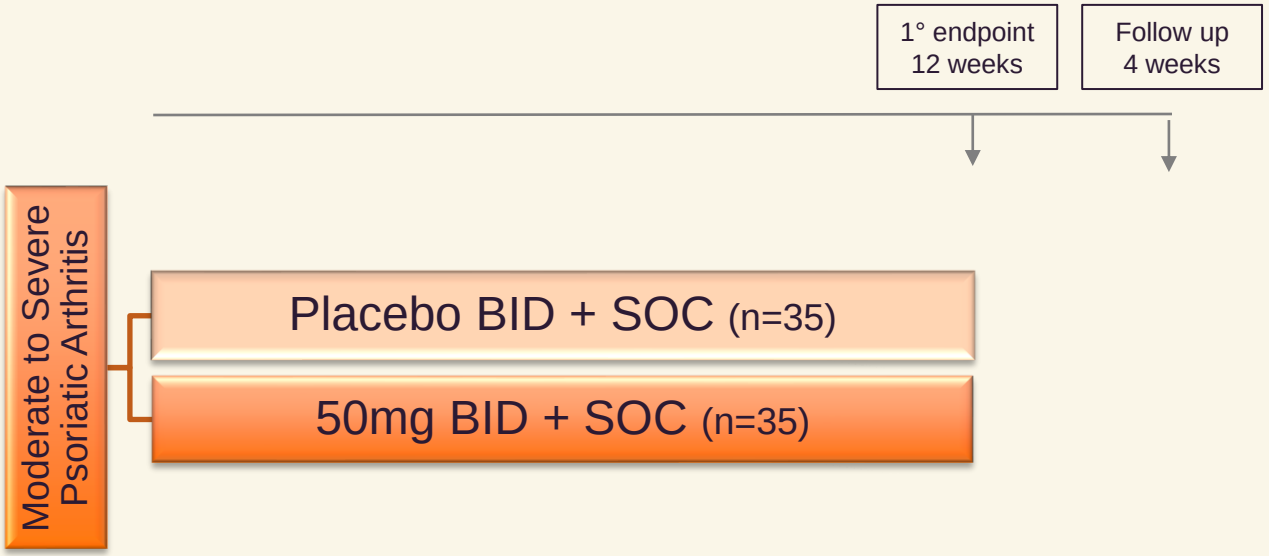
Zunsemetinib (ATI-450) Clinical Studies (2)

ATI-450-PsA-202: Adults with moderate to severe Psoriatic Arthritis



Primary Endpoint
- ACR 20 responders

Secondary Endpoints Include:
- ACR 50, 70
- Psoriasis IGA, PASI75
- Dactylitis, Enthesitis
- Safety
- PK + PD

KINect® Drug Discovery Platform

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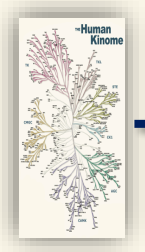
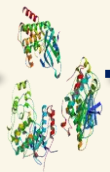
KINect® Platform
Developing Kinase Drug Candidates Rapidly & Efficiently

TARGET SELECTION & VALIDATION → **KINect® Platform – LEAD GENERATION** → **ASSET GENERATION**

Explore 500+ Kinases	Select Cysteine Kinases	Assess Target Confidence
		
>300 Cysteine Kinases	w/Published Crystal Structures	• Disease • Genetics • Safety • Distribution

Proprietary Portfolio
- MK2 Inhibitors
- JAK Inhibitors
- ITK Inhibitors

Strategic Partnerships
- Research
- Licensing
- Commercial

Proprietary Library:
High affinity/selective drug scaffolds

Faster Path:
Decrease time to Lead Optimization by half or more

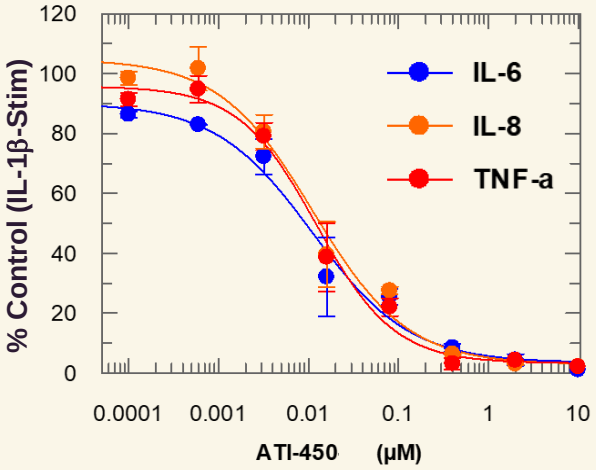
Multiple Approaches:
Design approach specific to each kinase

MK2 Inhibitor Program:

- Role of MK2 in IL-17 Biology

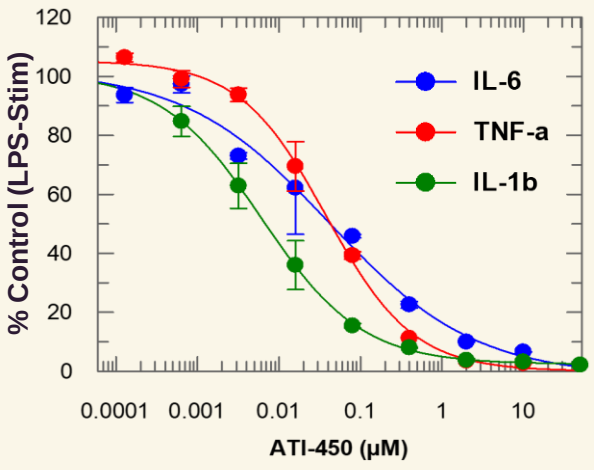
Zunsemetinib (ATI-450) Inhibited Proinflammatory Cytokine Production in Human Whole Blood

IL-1R: IL-1β-Stimulated HWB



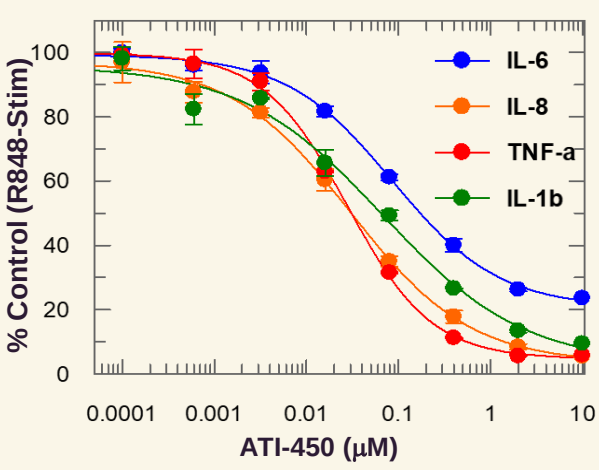
0 ATI-450 | 1hr 10ng/ml IL-1β | 5hr Cytokines quantified by MSD

TLR4: LPS-Stimulated HWB



0 ATI-450 | 1hr 100ng/ml LPS | 4hr Cytokines quantified by MSD

TLR7/8: R848-Stimulated HWB



0 ATI-450 | 1hr 0.5ug/ml R848 | 5hr Cytokines quantified by MSD

Zunsemetinib Inhibited Key Inflammatory Cytokines Induced by Multiple Disease Relevant Stimuli in HWB

HWB = Human Whole Blood
Data on file

Does Zunsemetinib Have a Role in IL-17 Biology?

- Understand the role of zunsemetinib in TH17 biology
  - ✓ Preclinical cellular studies executed to understand the role of MK2 and zunsemetinib in IL-17 production and signal transduction[1]
- If zunsemetinib regulates TH17 biology, it would provide:
  - ✓ additional mechanistic rationale for current indications: RA, HS, PsA
  - ✓ additional indications could be considered including ankylosing spondylitis
- Approach: assess impact of zunsemetinib on:
  - ✓ IL-17 production in CD4+ T cells
  - ✓ IL-17 stimulated protein phosphorylation and cytokine production

RA = rheumatoid arthritis; HS = hidradenitis suppurativa; PsA = psoriatic arthirtis

1. Data on file.

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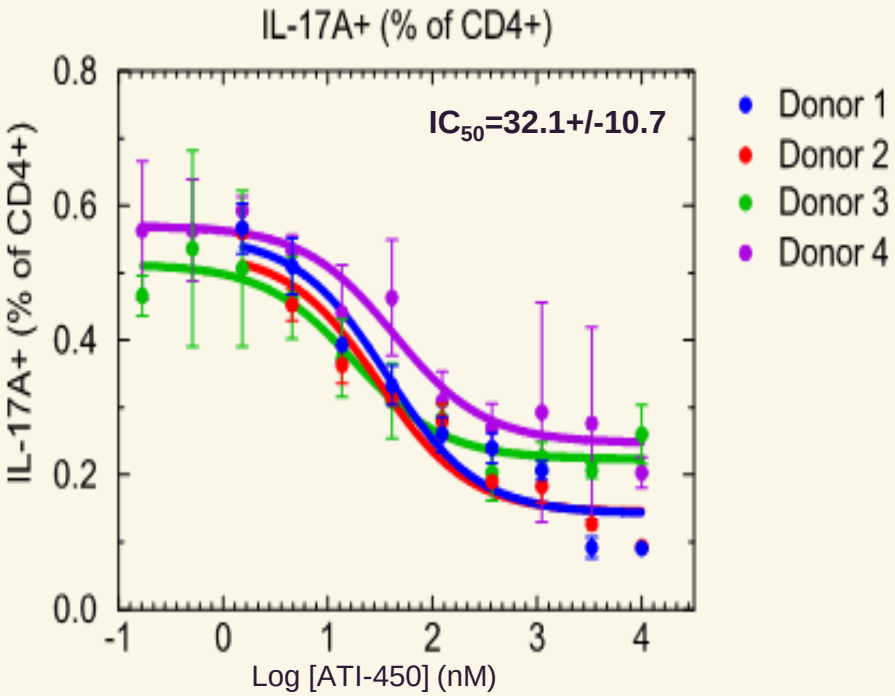
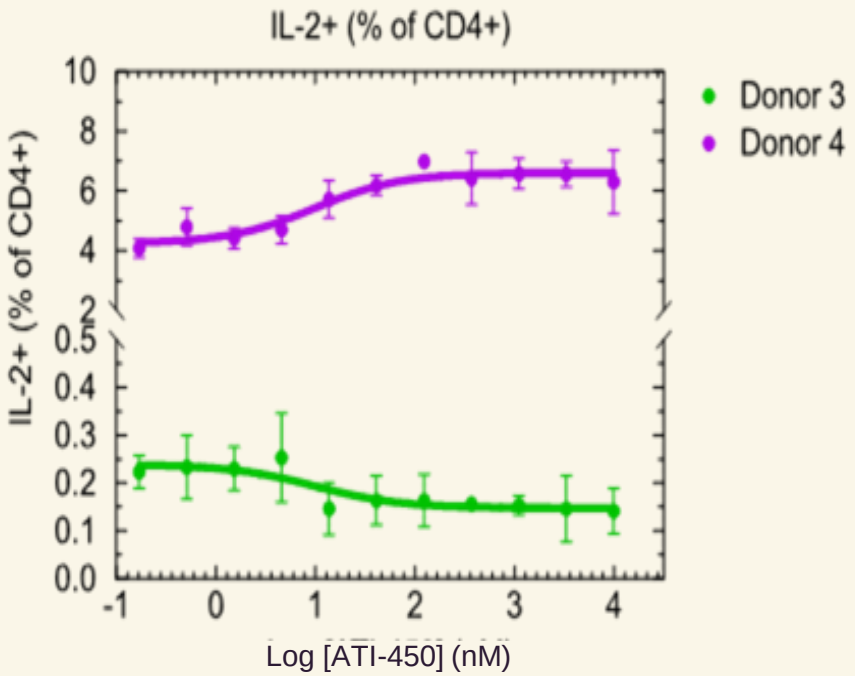
Impact of Zunsemetinib on IL-17 Production in Preclinical Human Cellular Studies



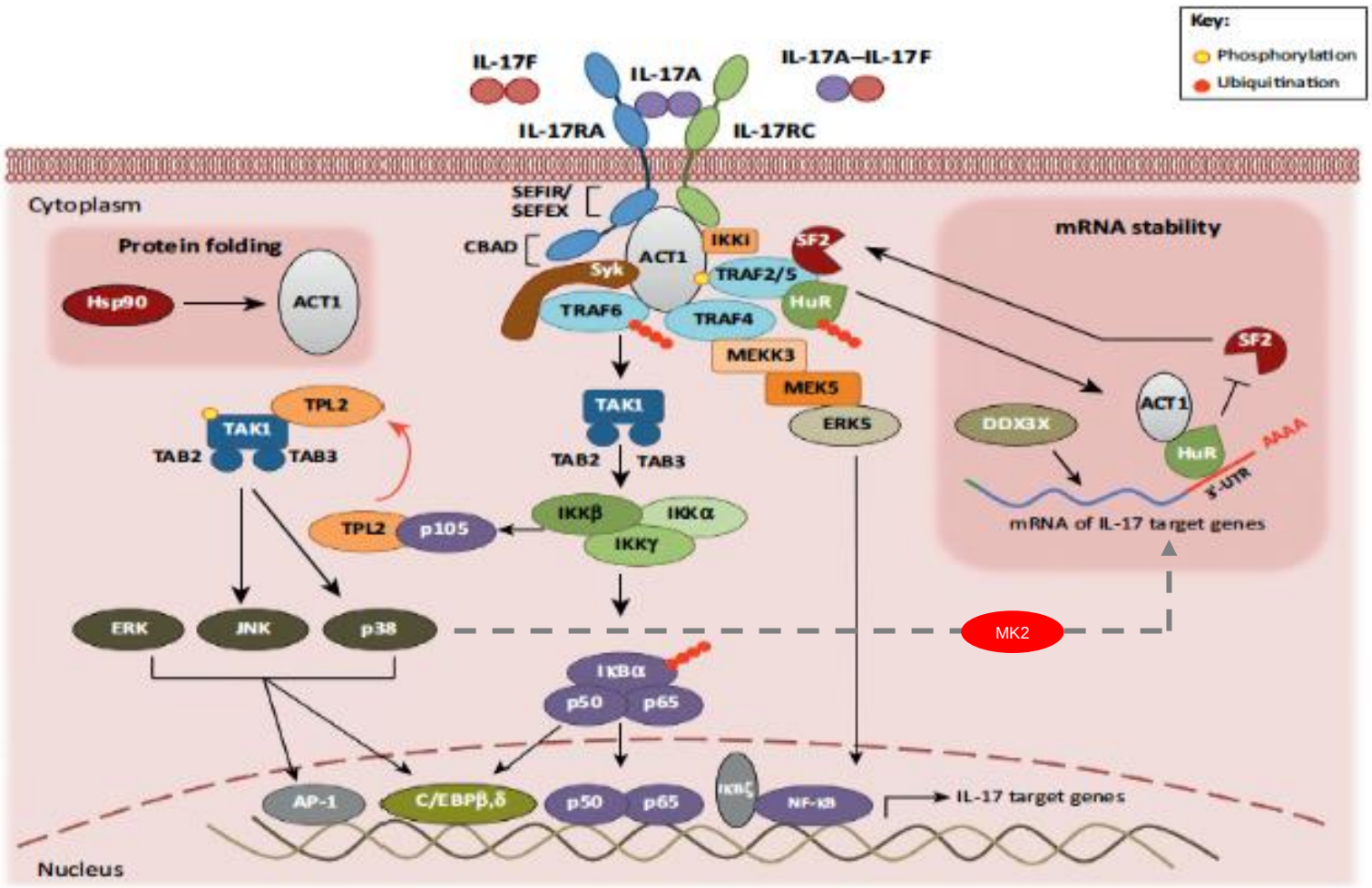


- hPBMC treated with antiCD3/28 for 72 hr
- Intracellular IL-17A and IL-2 measured in CD4+ cells by fluorescence activated cell sorting (FACS)

Zunsemetinib showed dose-dependent inhibition of IL-17A production with no effect on IL-2 production in preclinical human cellular studies

hPMBC = human peripheral blood mononuclear cells
Data on file.

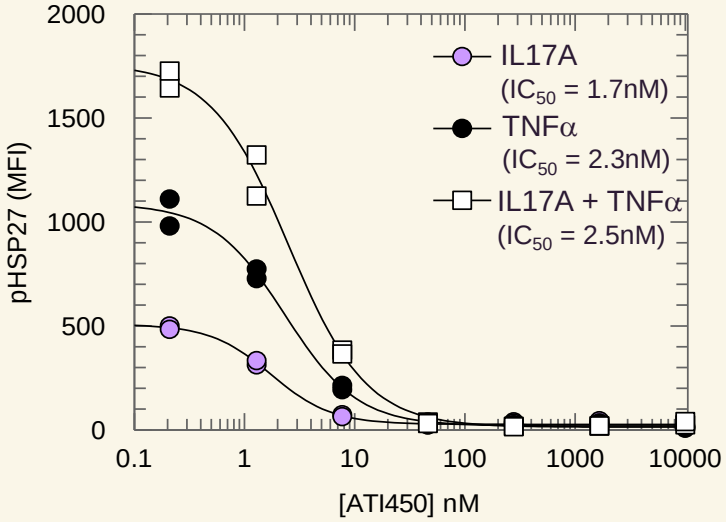
IL-17 Signal Transduction: Is MK2 Involved?



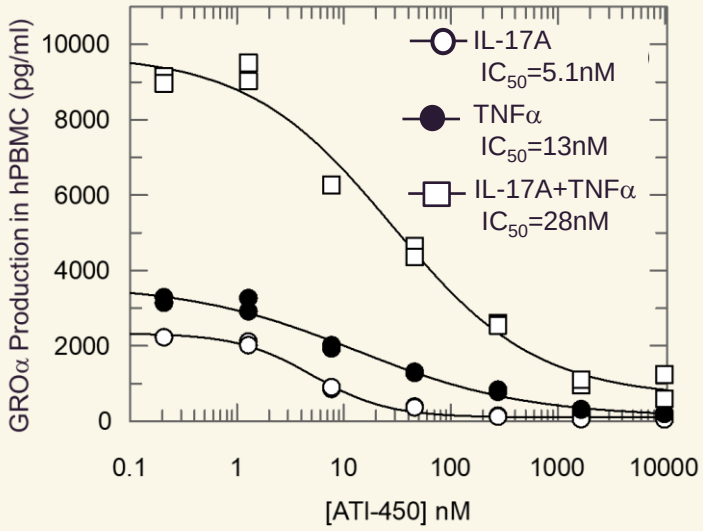
Adapted from Amatya N, et al. *Trends Immunol*. 2017 May;38(5):310-322.

Zunsemetinib Inhibited IL-17 Activation of the MK2 Pathway in Preclinical Human Cellular Studies

hDF cells: pHSP27



hPBMC: GROα Production



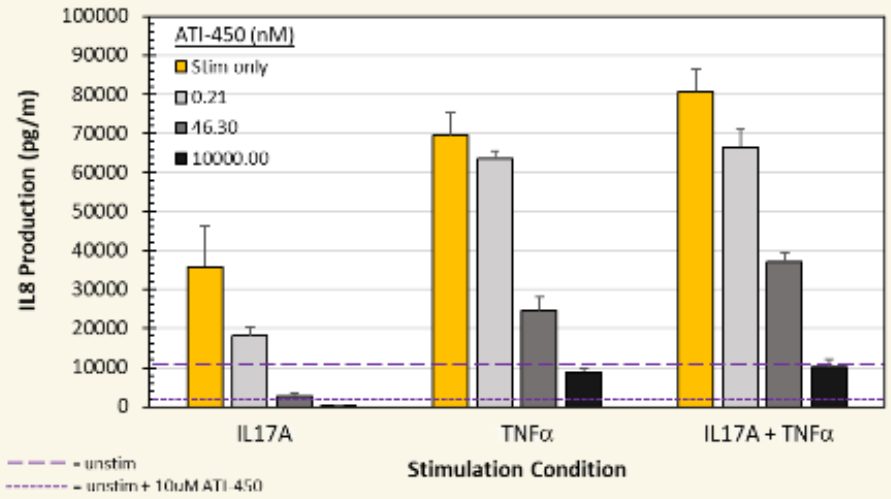
- Stimulation of hRASF (not shown) and hDF with IL-17A, TNFα, or a combination, induced HSP27 phosphorylation
- hPBMC stimulation with IL-17A, TNFα, or a combination, induced GROα production

Zunsemetinib concentration-dependently blocked both pHSP27 and GROα with low nanomolar IC_{50}'s in preclinical human cellular studies

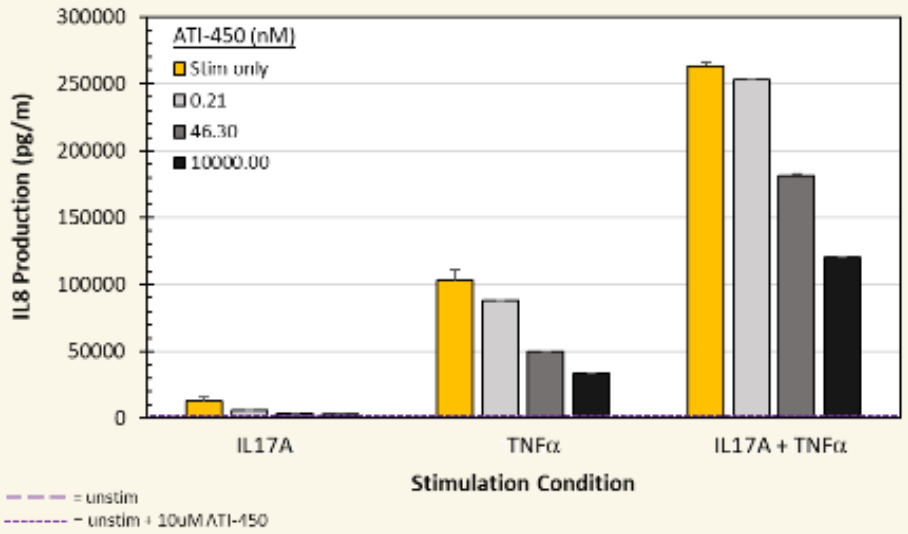
hRASF = human RA synovial fibroblasts; hDF = human dermal fibroblasts
Data on file.

Zunsemetinib Inhibited IL-17 Induced IL-8 in a Cell Dependent Manner in Preclinical Human Cellular Studies

hPBMC: IL-8



hRASF cells: IL-8



- IL-17A, TNFα, and IL-17A/TNFα stimulated IL-8 production in hPBMC and hRASF (shown above) and hDF (not shown)
- IL-17F activity also modulated by zunsemetinib (not shown)

Zunsemetinib inhibited IL-8 production induced by all stimulation conditions across the three cells types in preclinical human cellular studies

Data on file.

MK2 Inhibitor Program:

- ATI-2231: an MK2 Inhibitor for Oncology
  (Investigational Drug Candidate)

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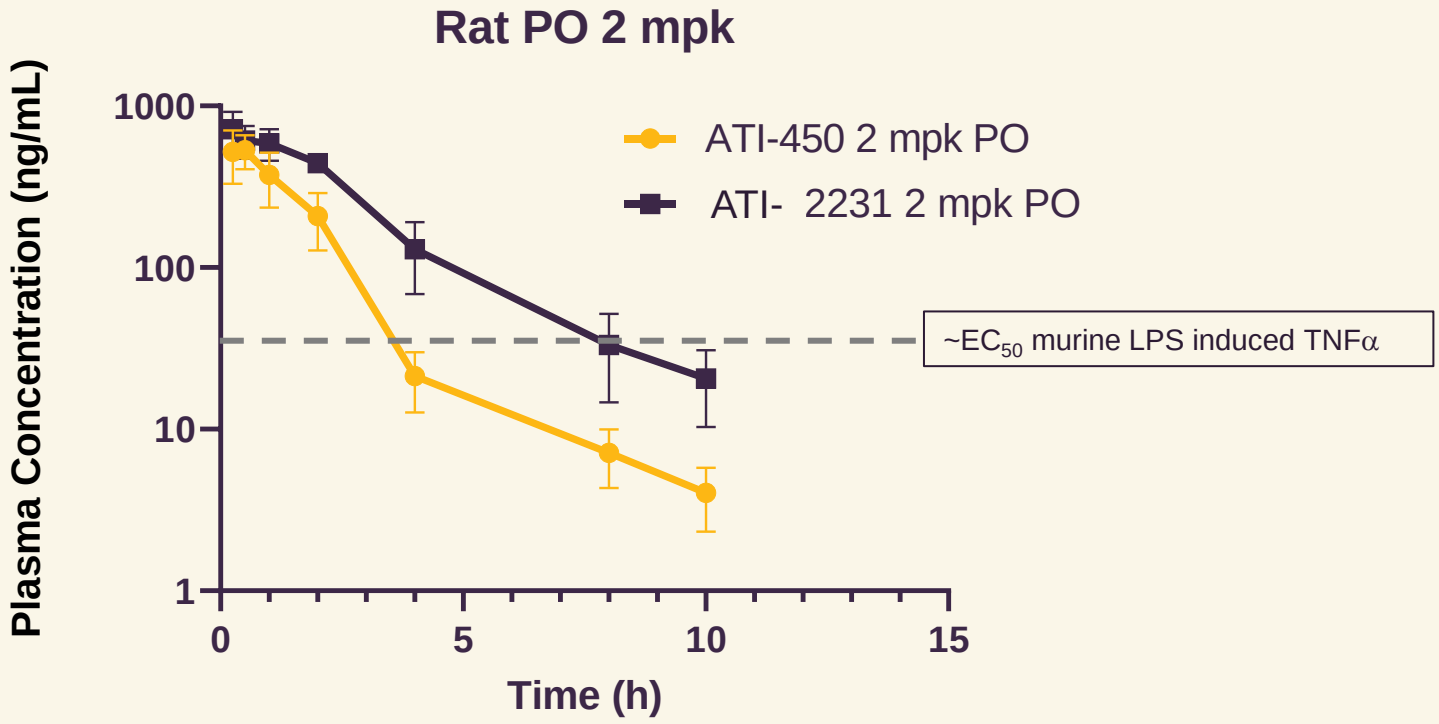
ATI-2231: a Novel MK2 Inhibitor

- Designed for decreased metabolism and clearance
- Preclinical biochemical/biological potency comparable to zunsemetinib
- Planned IND submission for oncology by end of 2022

Data on file.

ATI-2231: Potential for Differentiated PK Relative to Zunsemetinib

Rat Model



- ATI-2231 showed lower clearance and higher AUC in rats compared to zunsemetinib (ATI-450)
- Potential for differential dosing levels and intervals

Data on file.

ATI-2231: MK2 Inhibition and Target Selectivity

Enzyme Potency of ATI-2231 for the p38/MK2 Complex

Assay	ATI-2231 (IC_{50}, nM)	Zunsemetinib (IC_{50}, nM)
p38/MK2	4.9 (1.3*)	15.6 (1.5*)

* Geometric standard deviation

Selectivity Ratios Relative to p38/MK2 Complex Inhibition

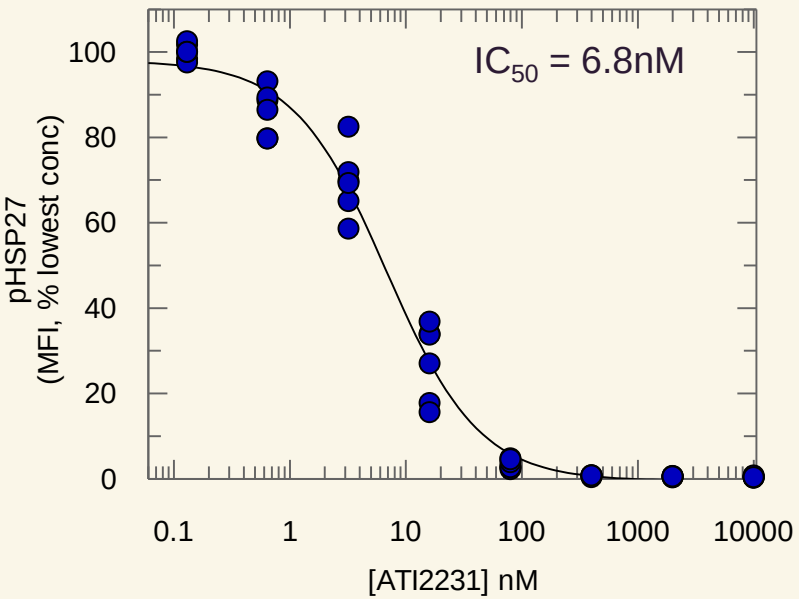
Inhibitor	p38/PRAK	p38	MK2
ATI-2231	1040x	51x	>4000x
Zunsemetinib	750x	51x	>550x

Data on file.

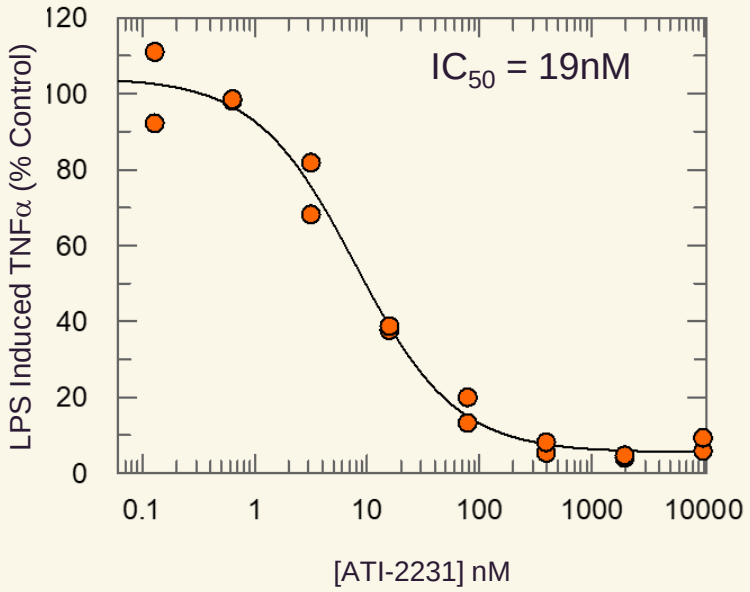
ATI-2231: Cytokine Inhibition from Human Whole Blood

Stimuli	IC_{50} (nM) from Stimulated Human Whole Blood (HWB)			
	TNFα	IL-1β	IL-6	IL-8
HWB + LPS	19 +/- 3	21 +/- 4	218 +/- 95	11 +/- 3
HWB + IL-1β	21 +/- 4	NA	16 +/- 9	19 +/- 5

ATI-2231 Inhibition of pHSP27



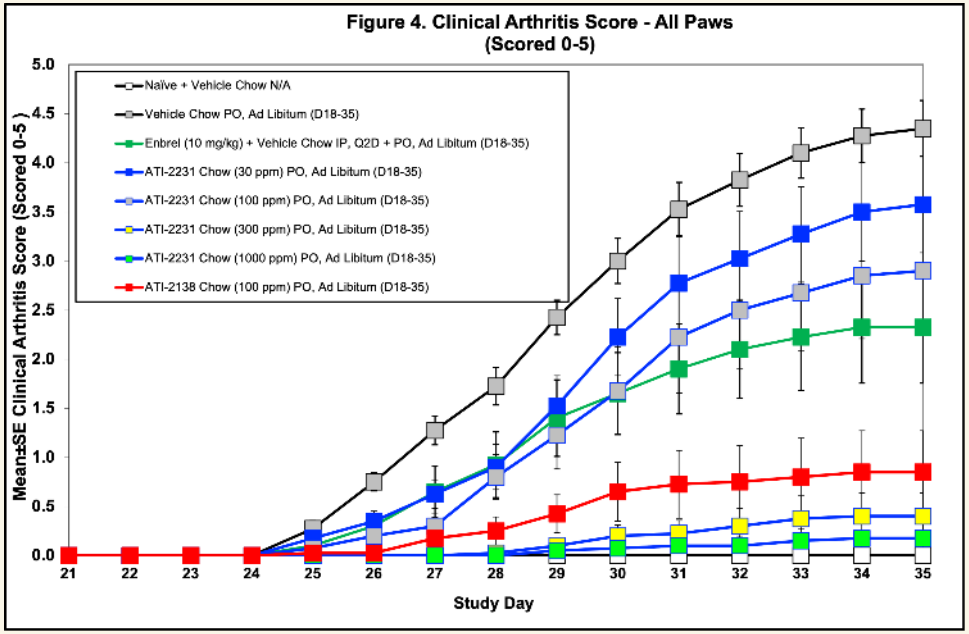
ATI-2231 Inhibition of TNFα

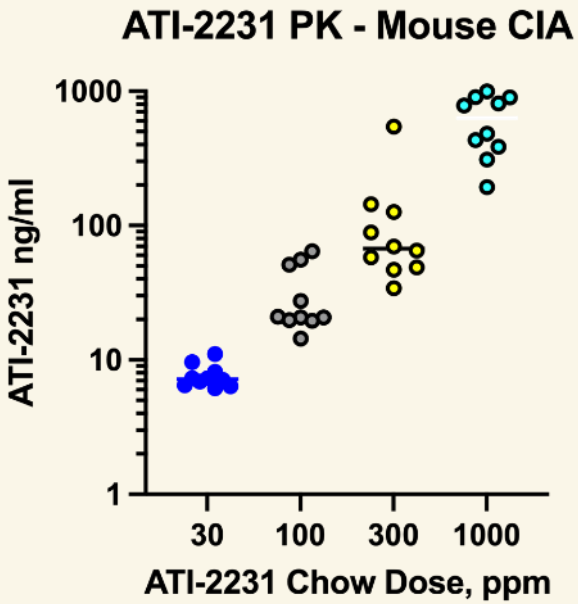


Data on file.

ATI-2231: Activity in Murine Collagen-Induced Arthritis

Mouse CIA ATI-2231 Clinical Score





- **Left:** Clinical Arthritis Score: collagen injections on days 1 and 21, dosing begins on day 18
- **Right:** Blood levels of ATI-2231 evaluated on the last day of the study

- **Dose-dependent activity observed with ATI-2231**
- **ATI-2231 superior to the Enbrel® (etanercept) comparator in this mouse model**
- **Activity observed at exposures of 20-100ng/ml**

* All trademarks are the property of their respective owners.
Data on file.

MK2: Distinct Mechanisms in Metastatic Breast Cancer (MBC) vs. Pancreatic Ductal Adenocarcinoma (PDAC)

Blocking Tumor Cell Survival (MBC) vs. Amplification of Cytotoxic Cell Death (PDAC)

- Tumors **induce** stromal cells in their environment to produce **cytokines** which act in an autocrine fashion to **promote tumor survival**[1]
- In MBC, it is this **induced cytokine** production that is **blocked** by MK2 inhibition, limiting **tumor cell survival**[1]

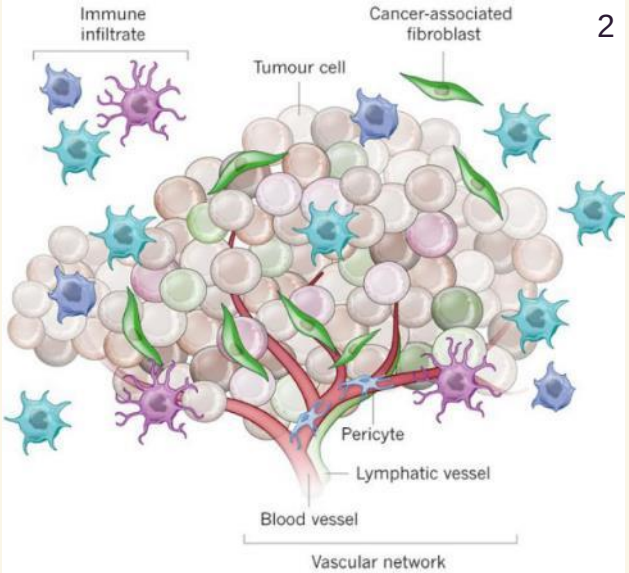


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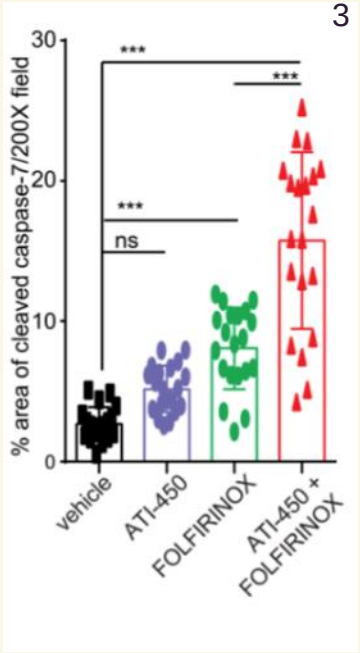
Figure 2: Cancer cells surrounded by microenvironment cells such as CAF's, immune cells, and pericytes. Image from Junttila and de Sauvage, 2013 with permission.

- PDAC treated with FOLFIRINOX (including **irinotecan)** activates a stress pathway that **requires MK2 for tumor cell survival**[3]
- **MK2 inhibitor** in the **presence of irinotecan** amplified **tumor death**[3]



3

Caspase-7 induction (marker of cell death) amplified when zunsemetinib (ATI-450) and FOLFIRINOX combined

1. Murali B, et al. *Cancer Res*. 2018 Oct 1;78(19):5618-5630.
2. Junttila MR, et al. *Nature*. 2013 Sep 19;501(7467):346-54.
3. Grierson P, et al. *Sci. Transl. Med*. 2021 Dec 1;13(622).

Metastatic Breast Cancer:
A Role for the MK2 Pathway in the Tumor Microenvironment

Sheila Stewart and Cynthia Ma, Washington University School of Medicine

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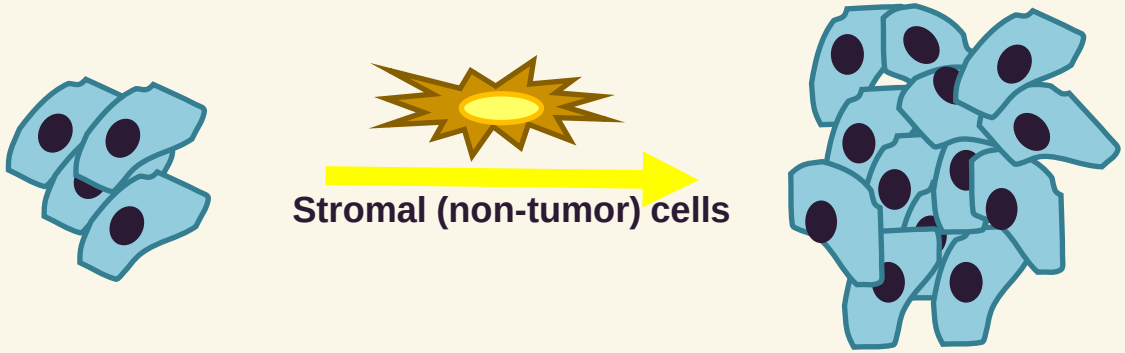
Stromal Cells Promote Tumorigenesis



Stromal cells increase

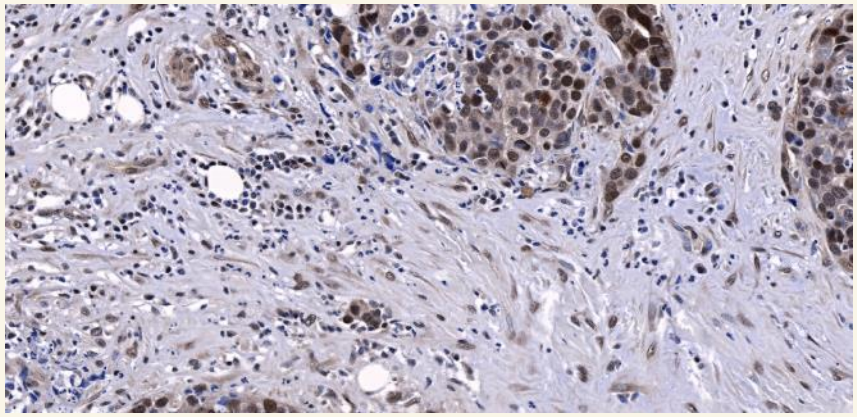
- tumor cell proliferation
- migration
- invasion
- angiogenesis
- immunosuppressive cells

Pro-tumor factors are expressed in the stromal compartment of human breast cancers and expression of a subset of those are critically dependent on MK2

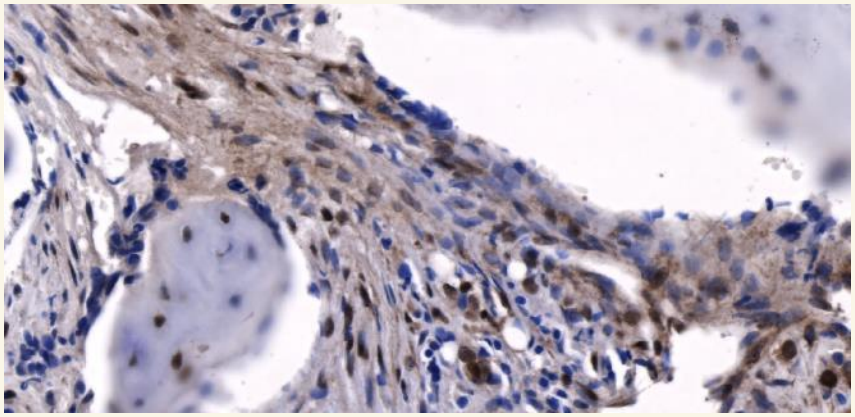
Avagliano A, et al. *Cancers*. 2020; 12(6):1697.

The MK2 Pathway is Activated in the Stroma of Both Primary Breast and Metastatic Bone Lesions

Breast Tumor



Metastatic Bone Tumor



- Immunohistochemistry reveals phospho-MK2 in primary tumors and metastatic bone lesions from the same patients
- Stromal derived factors that drive tumor growth depend on MK2 pathway signaling, therefore MK2i should block this effect

Stewart Lab, Washington University School of Medicine

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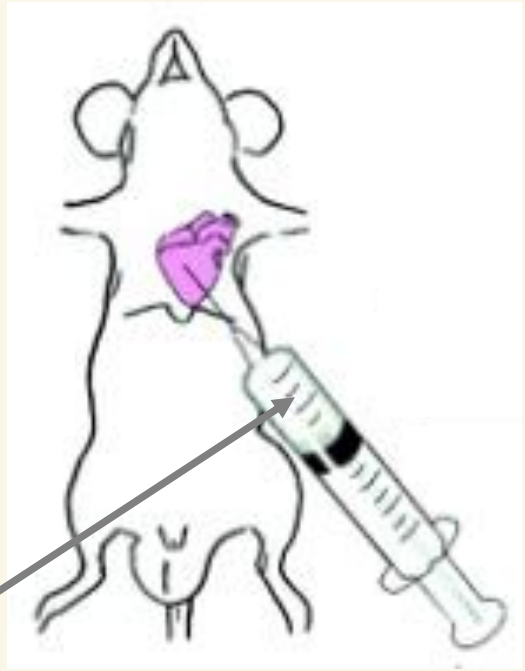
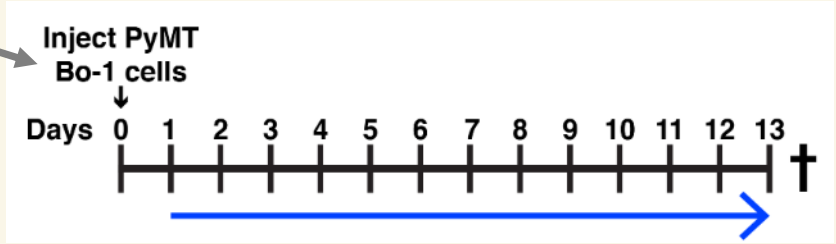
Modeling Bone and Visceral Metastasis in the Mouse

- 70% of all metastatic breast cancer patients harbor bone metastasis[1]
- Patients with bone metastases suffer numerous co-morbidities including significant risk for bone fractures[1]
- Currently no spontaneous mouse model exists to study bone metastasis
- A tumor cell intra-cardiac injection model allows tumor cells to seed into the bones and visceral organs[2]
- Bo-1 PyMT cells used to create metastatic breast cancer mouse model[3]

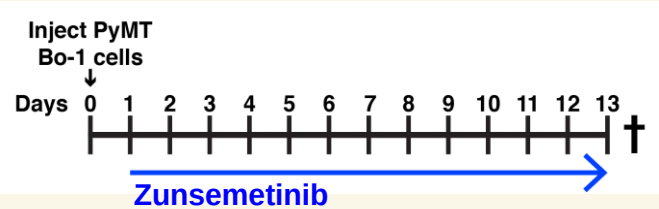
Intra-cardiac tumor cell injection model[4]



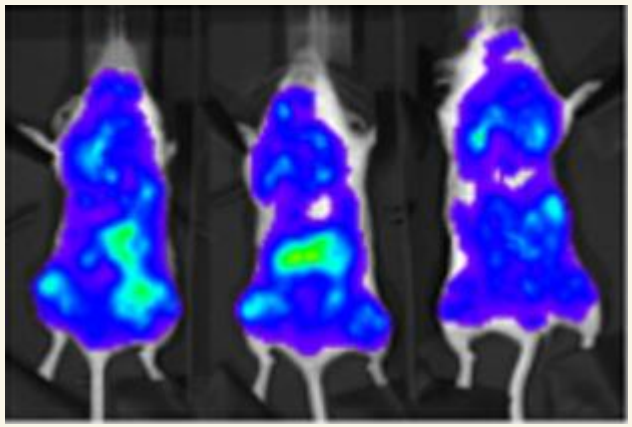


1. Monteran L, et al. *Sci Rep*. 2020;10:13838.
2. Murali B, et al. *Cancer Res*. 2018 Oct 1;78(19):5618-5630.
3. Su X, et al. *Cancer Res*. 2016 Jun 15;76(12):3484-95.
4. Stewart Lab, Washington University School of Medicine.

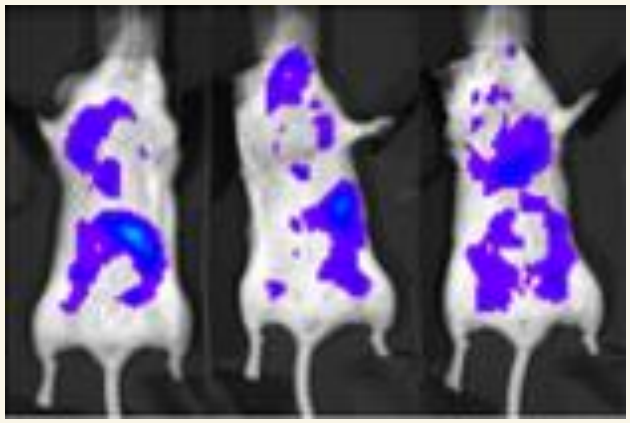
Zunsemetinib Reduced Breast Cancer Bone and Visceral Metastases in Mouse Model of Disease



Vehicle



Zunsemetinib



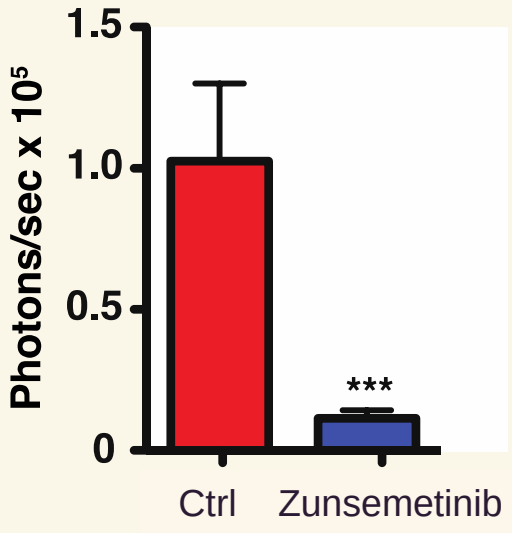
Murali B, et al. *Cancer Res*. 2018 Oct 1;78(19):5618-5630.

Affecting both tumor survival and bone disease in this mouse model was unprecedented in a single agent

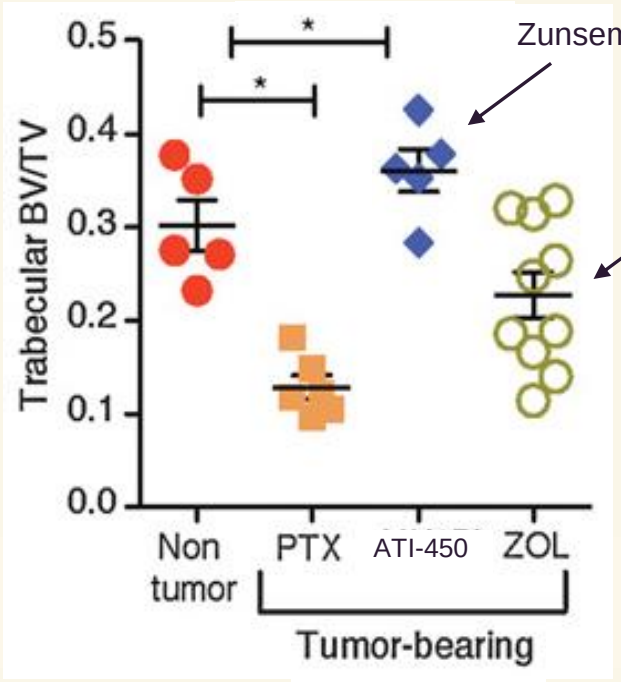
Zunsemetinib Reduced Breast Cancer Metastases and Preserved Bone

Murine Intra-cardiac Tumor Cell Injection Model

Bone Metastasis[1]



Trabecular Bone Volume[1]



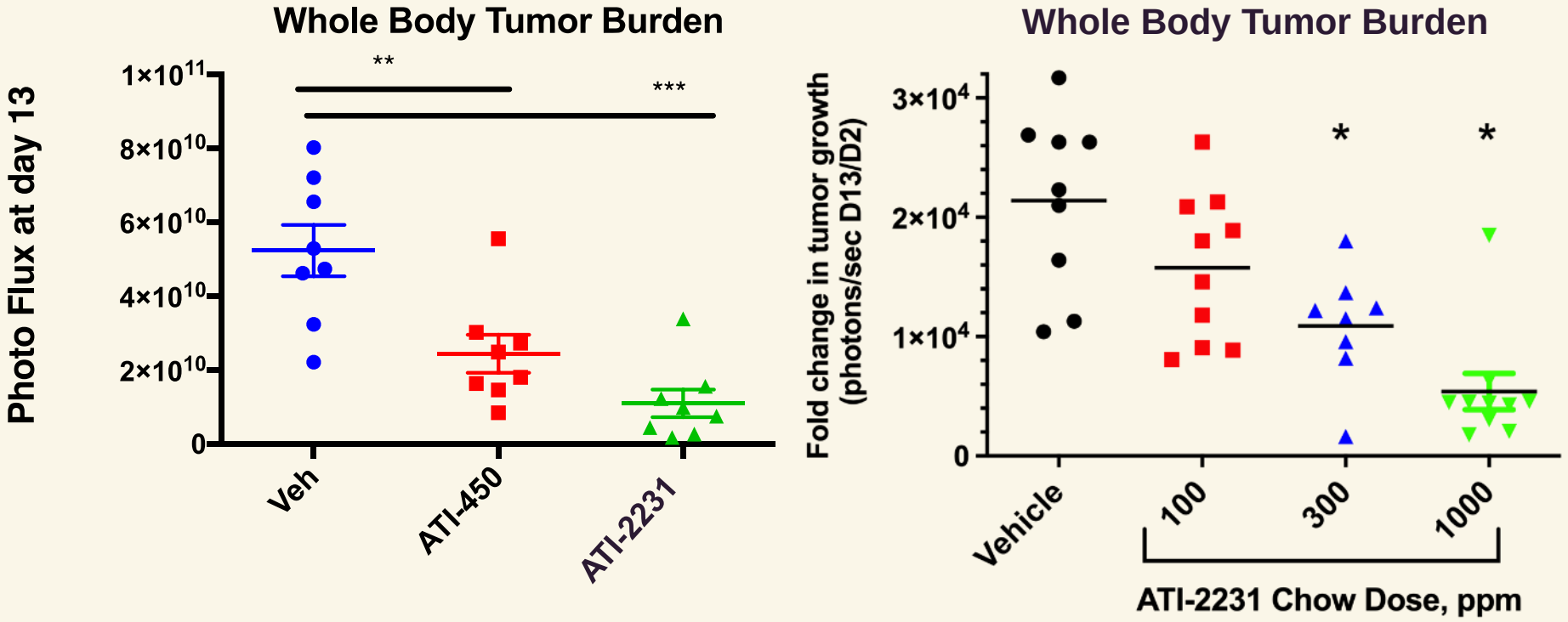
*Bone quality in untreated diseased animals was too low to measure (0.0 on the Y-axis)

Zunsemetinib preserved bone quality in the mouse model better than paclitaxel (PTX)[2] and as well as zoledronic acid (ZOL)[3], current standards of care, and prevented bone metastases in the mouse model

1. Murali B, et al. *Cancer Res*. 2018 Oct 1;78(19):5618-5630.
2. Sparano JA, et al. *N Engl J Med*. 2008 Apr 17;358(16):1663-71.
3. Polascik TJ, et al. *Ther Clin Risk Manag*. 2008;4(1):261-268.

Comparison of Zunsemetinib and ATI-2231 in Mouse MBC Model

Intra-cardiac injection of Bo-1 PyMT MBC Cells



Left: ATI-2231 and ATI-450 (zunsemetinib) reduced metastasis (both at 1000ppm) in mouse model

Right: ATI-2231 reduced metastasis in mouse model in a dose dependent manner

Stewart Lab, Washington University School of Medicine

Proposed Study:

A Phase 1/2 trial of ATI-2231 in combination with paclitaxel or capecitabine in patients with hormone receptor positive and HER2 negative metastatic breast cancer with bone metastasis

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The First Trial of ATI-2231 in Metastatic Breast Cancer

Plan:

- Investigator initiated study - DoD grant awarded to investigator
- Phase 1/2 trial of ATI-2231, in combination with paclitaxel or capecitabine, standards-of-care treatment, investigating PK, safety, impact on bone turnover and metastasis
- Trial will explore whether the addition of ATI-2231 can improve chemotherapy efficacy, delay disease progression and reduce chemotherapy and tumor-induced bone loss in patients with metastatic breast cancer

Inhibiting MK2 Blocked Tumor Growth in Models of PDAC

Kian Lim Lab, Washington University School of Medicine

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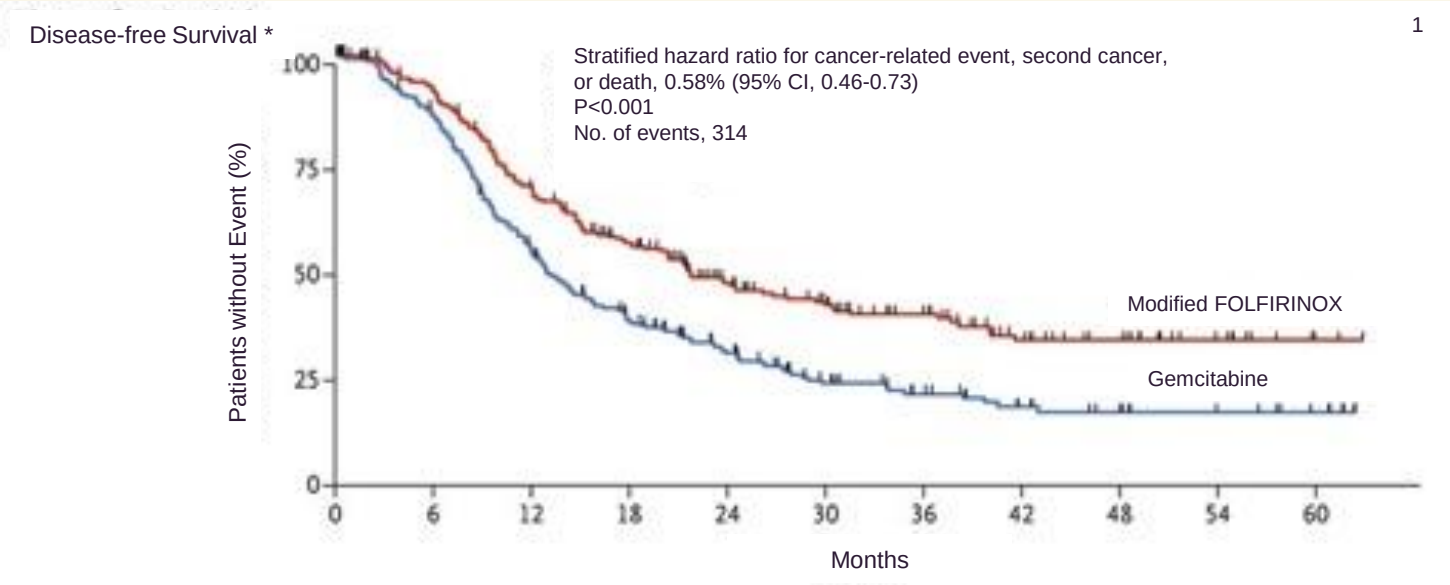
MK2 Inhibitor Pancreatic Cancer Update



- Standard of care for PDAC is switching from gemcitabine to FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, oxaliplatin) for preoperative, postoperative, first and second line therapy[1,2]
- Regimen has high toxicity, thus additional agents must be well tolerated and overcome resistance mechanisms[2]
- Irinotecan is the main driver of cellular stress/induced apoptosis - resistance to this stress in preclinical models was shown to be MK2-dependent[3]

Hypothesis: Reduced dose FOLFIRINOX plus MK2 inhibition may improve survival and reduce toxicity

1. Conroy T, et al. *N Engl J Med*. 2018 Dec 20;379(25):2395-2406.
2. Sohal DPS, et al. *J Clin Oncol*. 2020 Aug 5:JCO2001364.
3. Grierson P, et al. *Sci. Transl. Med*. 2021 Dec 1;13(622).

MK2 Inhibitor Value Proposition

- **Unmet Need:** There is a significant unmet need in PDAC as FOLFIRINOX is the preferred regimen but not all patients respond and response time is limited[1]
- **Unique MoA:** The MK2 MoA is to target a defense mechanism within PDAC cells that is incurred by FOLFIRINOX. There is currently no combination regimen based on FOLFIRINOX
- **Broad Utility:** Potential in preoperative, postoperative and metastatic settings and impact beyond PDAC

The preclinical studies supporting this approach are now accepted in **Science Translational Medicine**.[2]

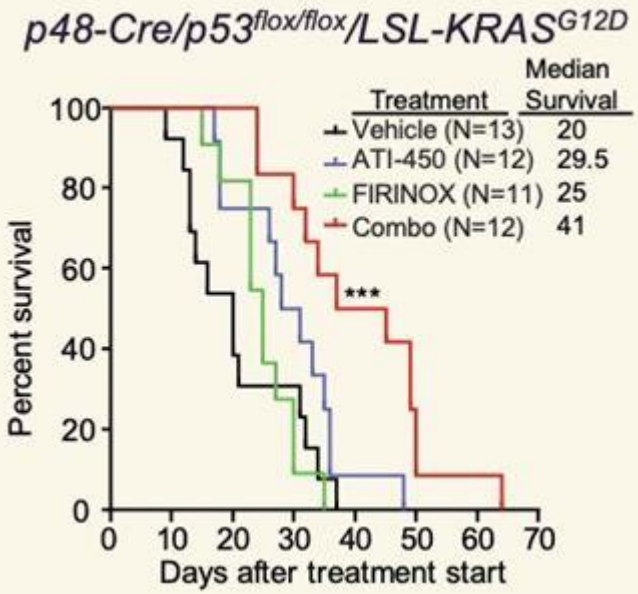
1. Conroy T, et al. *N Engl J Med*. 2018 Dec 20;379(25):2395-2406.
2. Grierson P, et al. *Sci. Transl. Med*. 2021 Dec 1;13(622).

MK2 Inhibition Rationale for Pancreatic Cancer

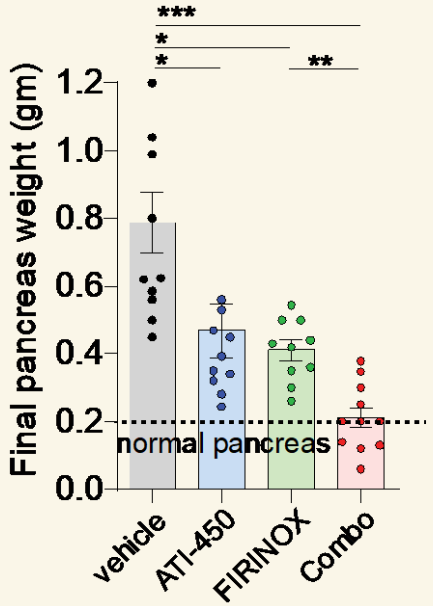
- Lim lab showed that chemotherapy induced stress in PDAC cells is driven by irinotecan and its active metabolite SN38[1]
- SN38 activates MK2/HSP27 pathway and blockade by MK2 RNAi or zunsemetinib increased SN38 induced apoptosis[1]
- Zunsemetinib evaluated in the “gold standard” KPPC model of PDAC[2]
- KPPC autochthonous tumor model[2]:
  - Cre promoter drives expression of the Kras G12D oncogene
  - KPPC mice have mutations in both alleles of p53 (the 2 P's)
- Autochthonous tumors genetically induced spontaneous pancreatic tumors and are believed to model human tumors more closely than transplanted tumors (xenografts)[2]

1. Grierson P, et al. *Sci. Transl. Med*. 2021 Dec 1;13(622).
2. Lee JW, et al. *Curr Protoc Pharmacol*. 2016 Jun 1;73:14.39.1-14.39.20.

Autochthonous Mouse Model of Pancreatic Cancer (KPPC)
Zunsemetinib (ATI-450) + Modified FOLFIRINOX Improved Activity



Pancreas Weight from KPPC Model



- Combination of zunsemetinib plus low dose FIRINOX improved survival compared to each drug alone in autochthonous mice
- Tumors isolated from KPPC mice treated with the combination were significantly smaller than those treated with FIRINOX alone

Data supports the investigation of the addition of MK2 inhibitor to FIRINOX in PDAC

Modified FOLFIRNOX (FIRINOX) = FOLFIRINOX without leucovorin

Grierson P, et al. *Sci. Transl. Med*. 2021 Dec 1;13(622).

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ATI-2138 (ITK/TXK/JAK3 (ITJ) Inhibitor)

(Investigational Drug Candidate)

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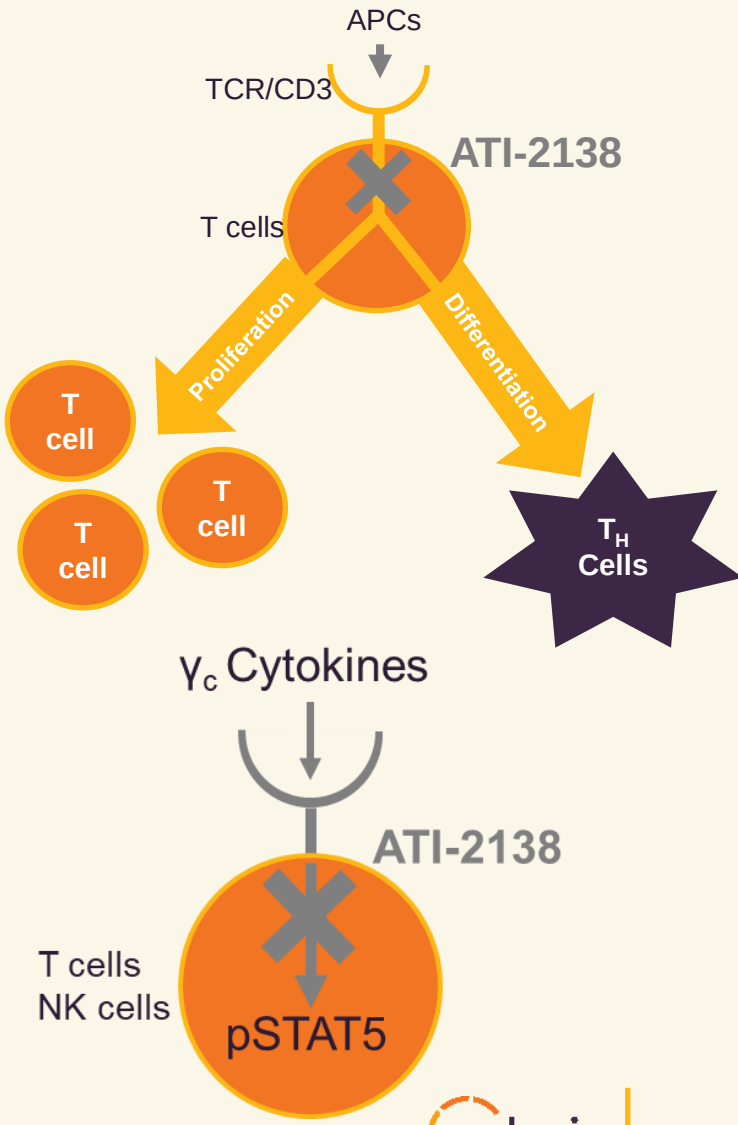
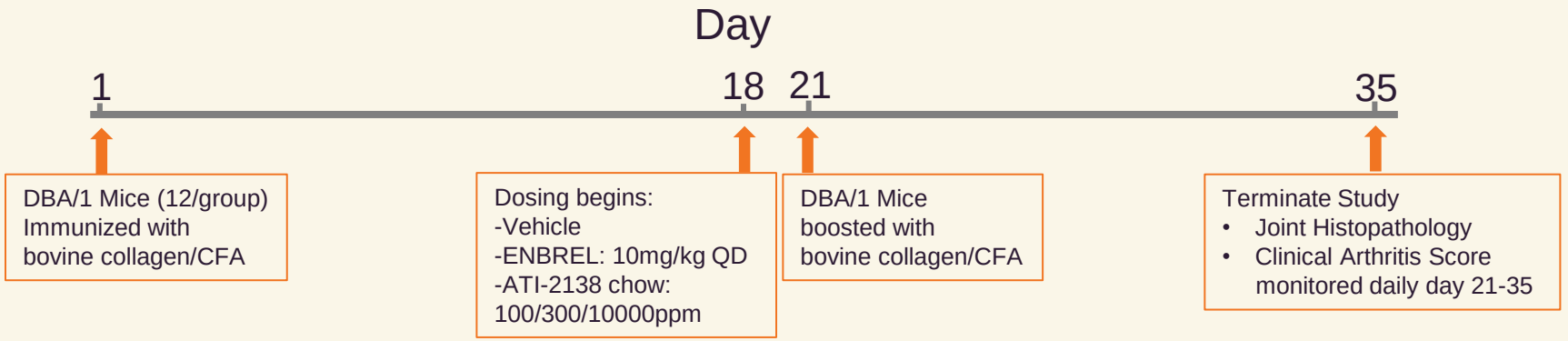
ATI-2138: Covalent ITJ Inhibitor

- ATI-2138 covalently blocks ITJ[1]
  - ✓ Potential for synergistic efficacy
    - ITK/TXK required for T-cell receptor (TCR) signaling
    - JAK3 required for γc cytokines (IL-2/4/7/9/15/21)
  - ✓ PD effects persist after plasma clearance
- ATI-2138 is selective for T-cell signaling[2,3]
  - ✓ Drugs like cyclosporine (CsA) inhibit calcineurin which is widely expressed
  - ✓ ATI-2138 targets unique kinases expressed only in immune cells
- ATI-2138 may potentially treat T-cell mediated autoimmune diseases[4,5]

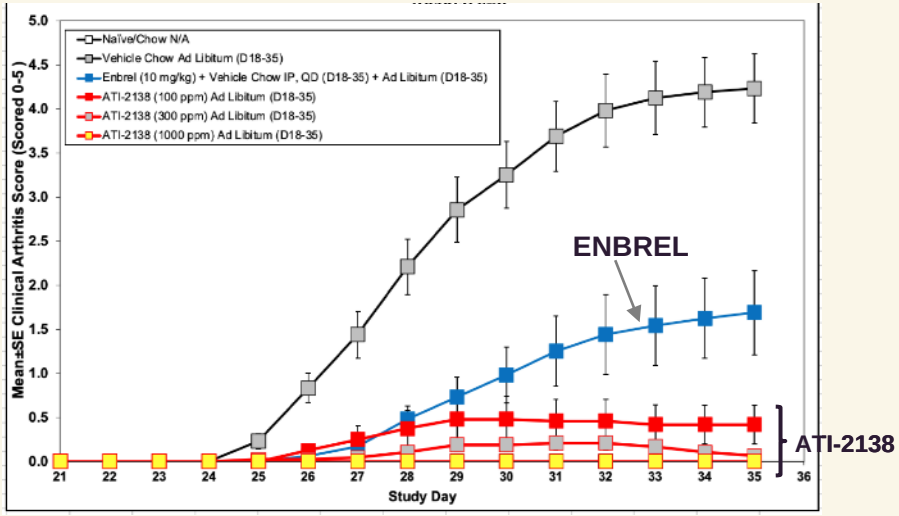


1. Data on file.
2. Graham RM. *Cleve Clin J Med.* 1994;61(4):308-313.
3. Siliciano JD, et al. *Proc Natl Acad Sci U S A*. 1992;89(23):11194–11198.
4. Robinson MF, et al. [published online ahead of print, 2020 May 18]. *Arthritis Rheumatol*. 2020.
5. Russell SM, et al. *Science*. 1995;270(5237):797-800.

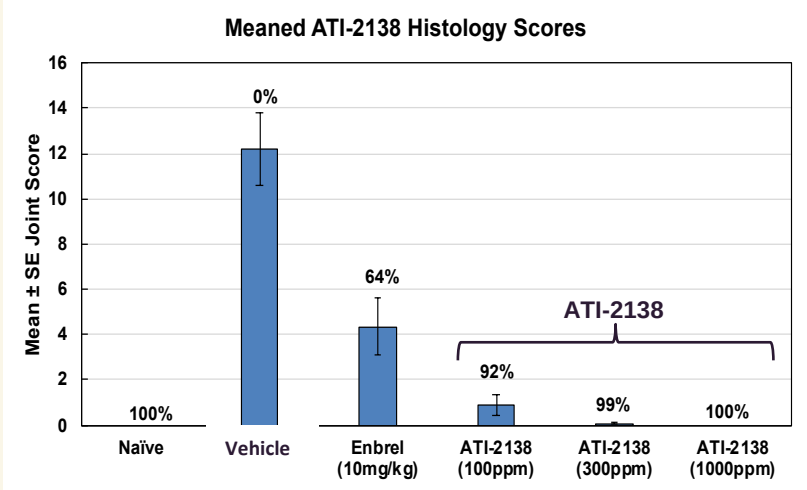
Mouse Model: ATI-2138 Showed Activity in mCIA



Clinical Arthritis Score



Joint Histology Score



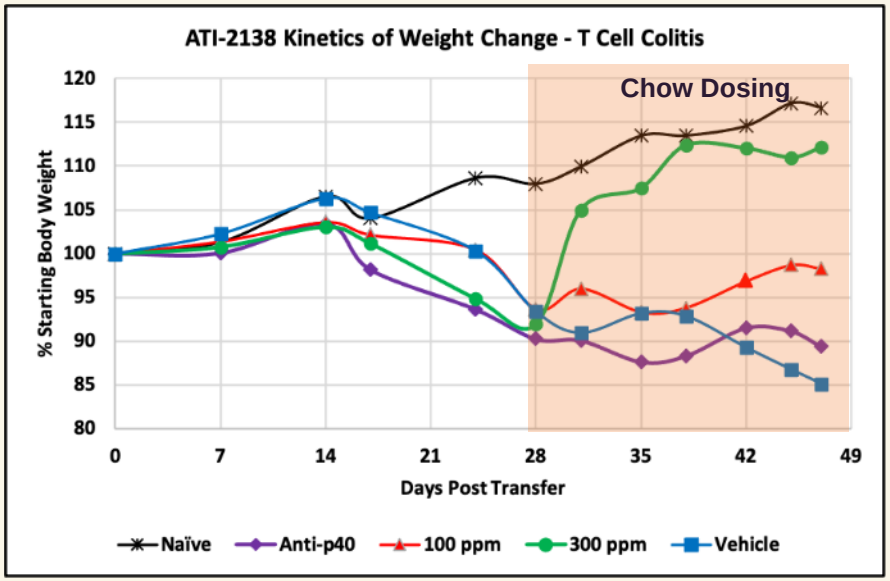
In the gold standard mCIA model, ATI-2138 demonstrated activity superior to Enbrel® (etanercept)

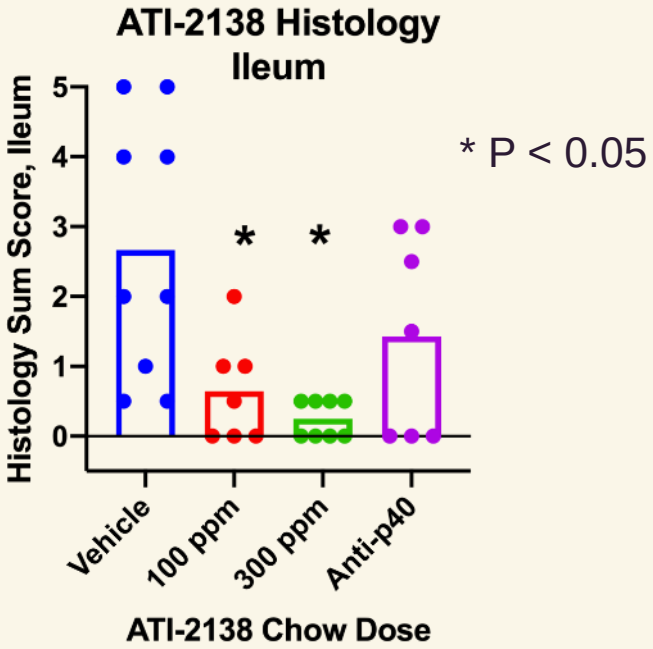
Data on file.

Mouse Model: ATI-2138 - T Cell Transfer Colitis

Day 0 — 28 — 47

- Day 0: $CD4^{+}CD45RB^{high}$ naïve T cells IP injected to SCID mice
- Day 28: Randomize/Dosing begins
  - Control Chow
  - ATI-2138: 100 or 300ppm
  - Anti-p40: 0.5mg, 2x/week
- Day 47: Terminate Study
  - Colon and ileum harvested for histology and cytokines





* P < 0.05

- 300 ppm chow dose of ATI-2138 reversed weight loss trend in disease model to match naïve controls
- 100 and 300 ppm chow doses were effective in preventing tissue damage in the ileum by histology

Data on file.

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ATI-2138: Phase 1 Clinical Plan

- Placebo-controlled, randomized, observer-blind single ascending dose trial in healthy volunteers
  - ✓ Study initiation expected December 2021
  - ✓ Endpoints
    - Safety/tolerability
    - Pharmacokinetics
    - Pharmacodynamic effects on T-Cell Receptor and JAK3/STAT-5 pathways
    - Food effect
- Placebo-controlled, randomized, observer-blind multiple ascending dose trial in psoriasis patients
  - ✓ Endpoints
    - Safety/tolerability
    - Pharmacokinetics/pharmacodynamics
    - Early signs of efficacy

Oral Gut-Biased JAK Inhibitors for Inflammatory Bowel Disease:

CDD-2603 and CDD-2676 Development Candidates

(Investigational Drug Candidates)

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Drugs for Inflammatory Bowel Disease (IBD)

- Autoimmune diseases are most commonly treated with broadly immune suppressive drugs (e.g., steroids, JAK inhibitors, anti-TNFα biologics) with systemic effects[1]
- Delivering drugs locally to site of inflammation has been effective with limited systemic effects[1]:
  - ✓Inhaled corticosteroids for asthma
  - ✓Budesonide enema for ulcerative colitis
- **Hypothesis:** Development of an orally administered gut-biased drug that can be designed with limited distribution outside the intestines may offer efficacy and convenience in IBD - with limited systemic immune suppression

1. Damsky W, et al. *J Allergy Clin Immunol*. 2021 Mar;147(3):814-826.

JAK Inhibitors for IBD

- Xeljanz® (tofacitinib) approved for ulcerative colitis (UC)[1], fails initial trials in Crohn's disease (CD)[2]
  - ✓ 9/2021: Updated FDA Warnings for all JAKi: Heart-related events such as MI/stroke, cancer, blood clots, and death with arthritis and ulcerative colitis medicines[3]
- TD-1473: Theravance publishes preclinical data with gut-selective pan-JAK inhibitor (TD-1473) predicting it could have efficacy/minimal systemic side effects[4]
  - ✓ *In vivo* activity evaluated in the murine oxazalone damage model with prophylactic dosing

Cellular potency of TD-1473 and Xeljanz® (tofacitinib) broadly equivalent[5]

	Human PBMC IC_{50}, nM			
	JAK1/3	**JAK1/2**	**Tyk2/JAK2**	**JAK2**
	IL-2	**IFNγ**	**IL-12**	**GM-CSF**
TD-1473	**31**	**29**	**387**	**59**
Tofacitinib	**11**	**64**	**534**	**224**

1. https://www.pfizer.com/news/press-release/press-release-detail/pfizer_announces_u_s_fda_approves_xeljanz_tofacitinib_for_the_treatment_of_moderately_to_severely_active_ulcerative_colitis-0. Last Accessed November 23, 2021.
2. Panés J, et al. *Gut*. 2017 Jun;66(6):1049-1059.
3. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death. Last Accessed November 23, 2021.
4. Sandborn WJ, et al. *J Crohns Colitis*. 2020 Sep 16;14(9):1202-1213.
5. Data on file.

GB Candidate Identification Strategy

1. **Design compounds with gut-biased potential**
   - Potent against JAK kinases
   - Low-moderate permeability
   - Lipophilic with high rates of efflux
   - Moderate metabolic stability
2. ***In vivo* testing in ”gold standard” model of IBD**
   - T cell adoptive transfer (TCT) model of colitis
   - Histological protection of gut tissue is key measure of efficacy
   - Comparison to tofacitinib at relevant exposures
   - Comparison to TD-1473 at multiple doses
3. **Demonstration of minimal systemic immune activity**
   - *Ex vivo* stimulation of blood immune cells from TCT
   - Activation marker status of transferred CD4 cells
   - Measurement of gut and plasma exposure

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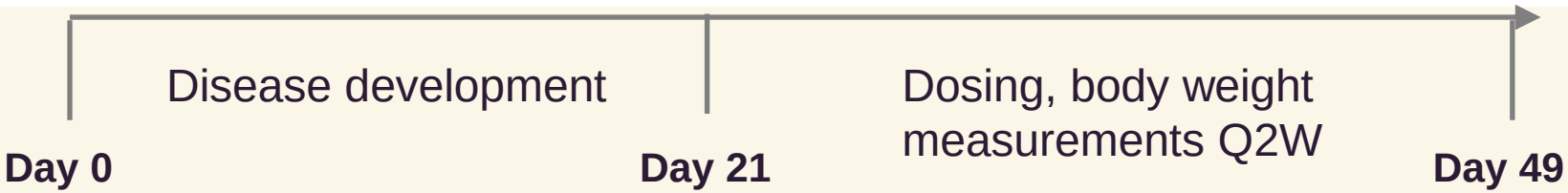
T Cell Adoptive Transfer (TCT) Mouse Model and Readouts



- **Day 0:** Naïve T cells purified using CD62L column method* and transferred into BALB/c SCID mice
- **Day 0 – 21**: In the absence of regulatory T cells, transferred naïve T cells react to microbiome at barrier surfaces, inducing colitis and weight loss
- **Day 21:** Animals are randomized to dose groups based on body weight, with drug administered admixed in chow (minimal handling)
- **Day 49:** Study terminated – tissues analyzed for local vs. systemic effects
  - *Ex vivo* stimulation of blood with IL-2/IL-12 and analysis of signaling blockade (pSTAT5/pSTAT4)
  - Splenic CD4 cells analyzed for levels of CD62L/CD25
  - Plasma drug levels
  - Histological scoring of colon and ileum

Strauch UG, et al. *Gut* 2005;54:1546-1552.

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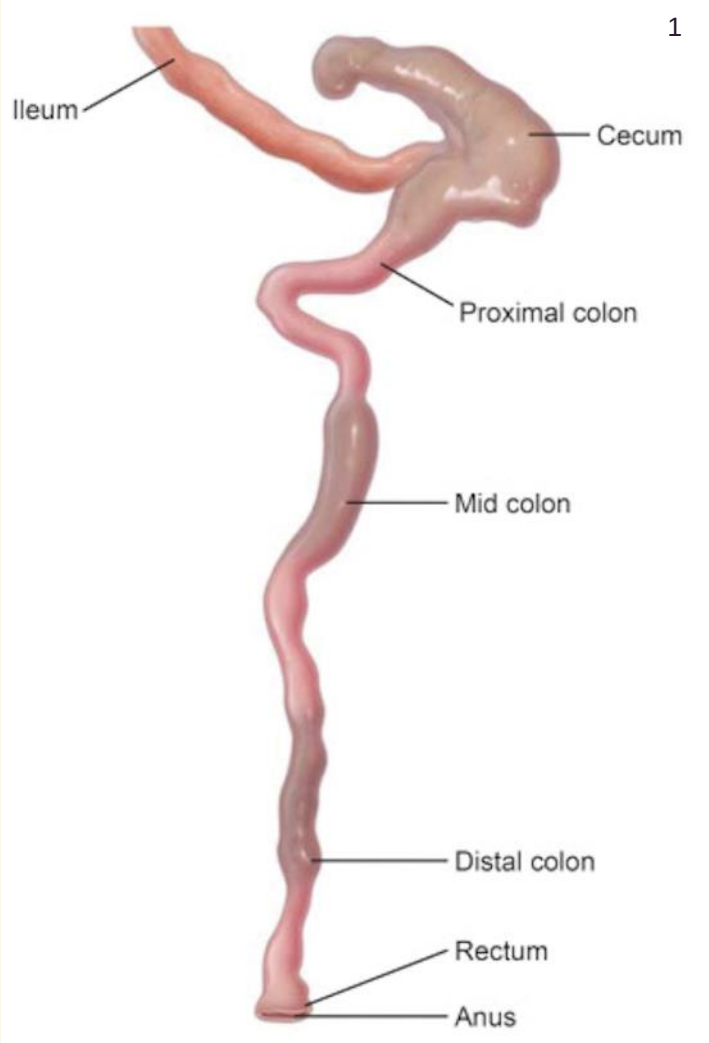
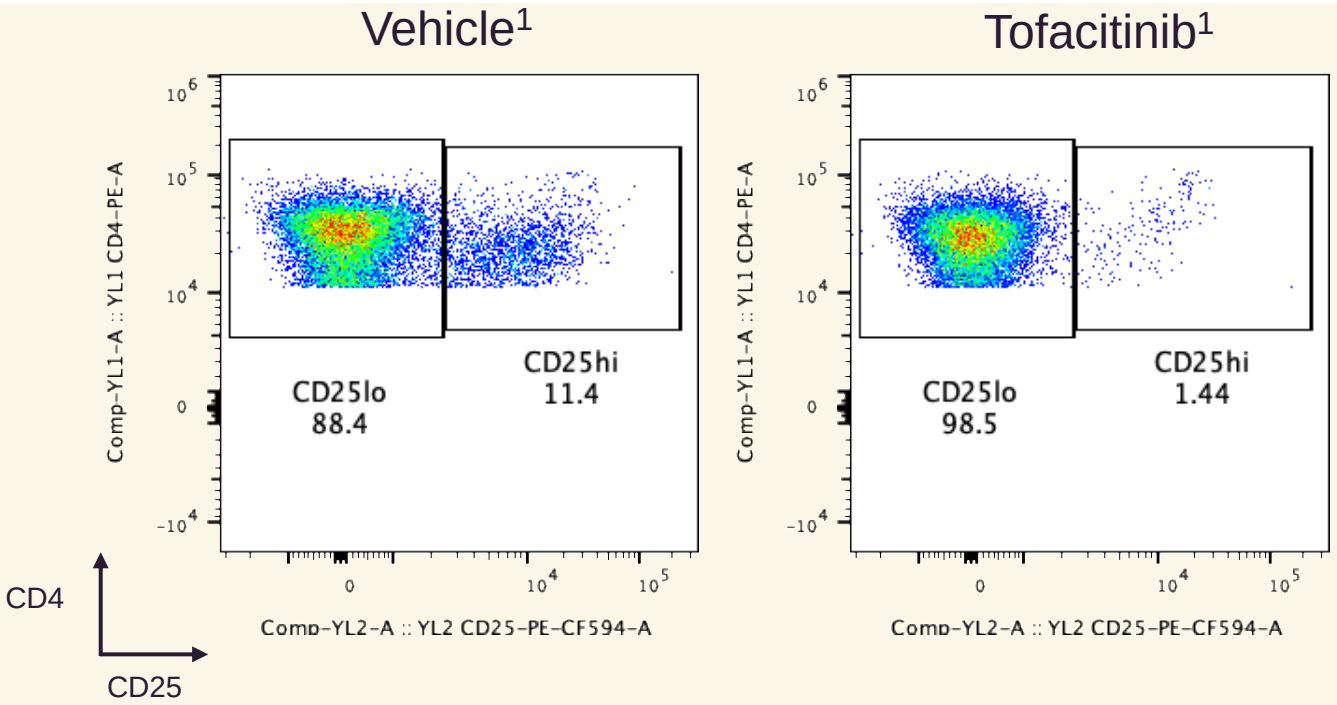
Intestinal Geography 101



- TCT model primarily thought of as UC model (colon damage), but damage also seen in the ileum – thus relevant to CD as well[2]
- CD can occur throughout the digestive system, with extra-GI manifestations common[2]
- Drug distribution may impact which form of IBD is most likely to respond to a particular drug
- Histology from each following study scored from ileum (I), proximal colon (P) and distal colon (D)

1. Treuting P, et al. *Comparative Anatomy and Histology.* 2018: 213-228.
2, Maxwell JR, et al. *Curr Protoc Pharmacol*. 2009 Dec;Chapter 5:Unit5.58.

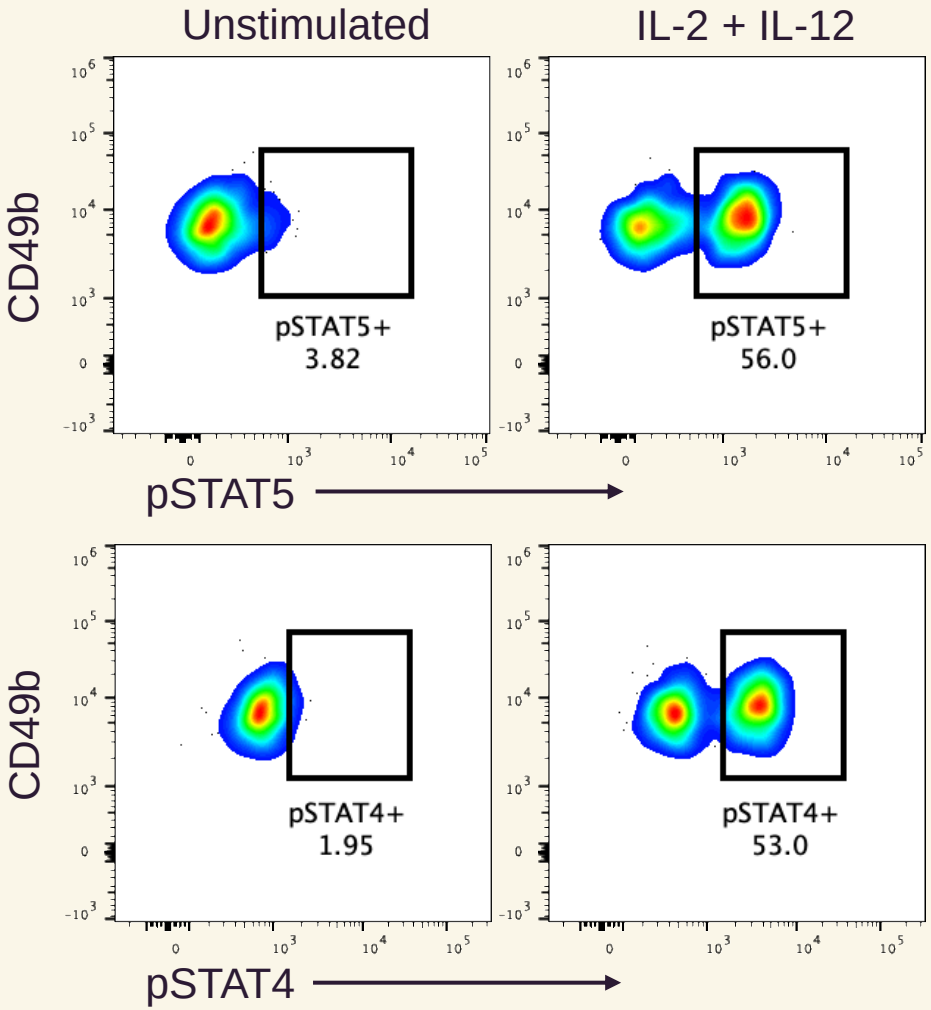
Evaluation of Systemic Effects in Mouse Model - Spleen



- CD62Lhi (L-selectin) naïve T cells are transferred into SCID mice[2]
- Over course of 7-week study, cells become activated in response to signals at various barrier surfaces (gut, lung, spleen)
- **Left**: Activation resulted in increased cell surface expression of CD25 (IL-2 receptor)
- **Right**: Reduction of CD25 (high expression) in peripheral lymphoid organs (spleen) by tofacitinib suggests drug is acting systemically

1. Data on file
2. Mudter J, et al. *Pathobiology*. 2002;70:170-176.

Evaluation of Systemic Effects in Mouse Model - Blood



- At study end, after 4 weeks of dosing – blood is stimulated with IL-2 and IL-12 for 30 min
- FACS analysis identifies NK cells (CD49b+) or T cells (CD4+) and pSTAT5 and pSTAT4
- Figure at left showed that >50% of NK cells in blood express these pSTATs after stimulation
- Decrease in percentage of cells that express these in response to IL-2/12 measured in drug-treated animals and taken as measure of systemic effects
- Blood PK measured

Data on file.

Compound Testing in Mouse Models

- **Positive control:** Tofacitinib dosing was optimized in the TCT model to be commensurate with its dosing clinically
- **Theravance** drug candidate: TD-1473
- **Aclaris** development candidates:

  ✓CDD-2603 and CDD-2676
- All compounds run twice in TCT model, with histological endpoints and systemic effects measured in all studies
- All groups had ten animals, and all compounds were run at multiple doses

TD-1473 created based on Patent No. WO 2016191524

Data on file.

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Xeljanz® (tofacitinib), an FDA Approved JAK Inhibitor for the Treatment of UC

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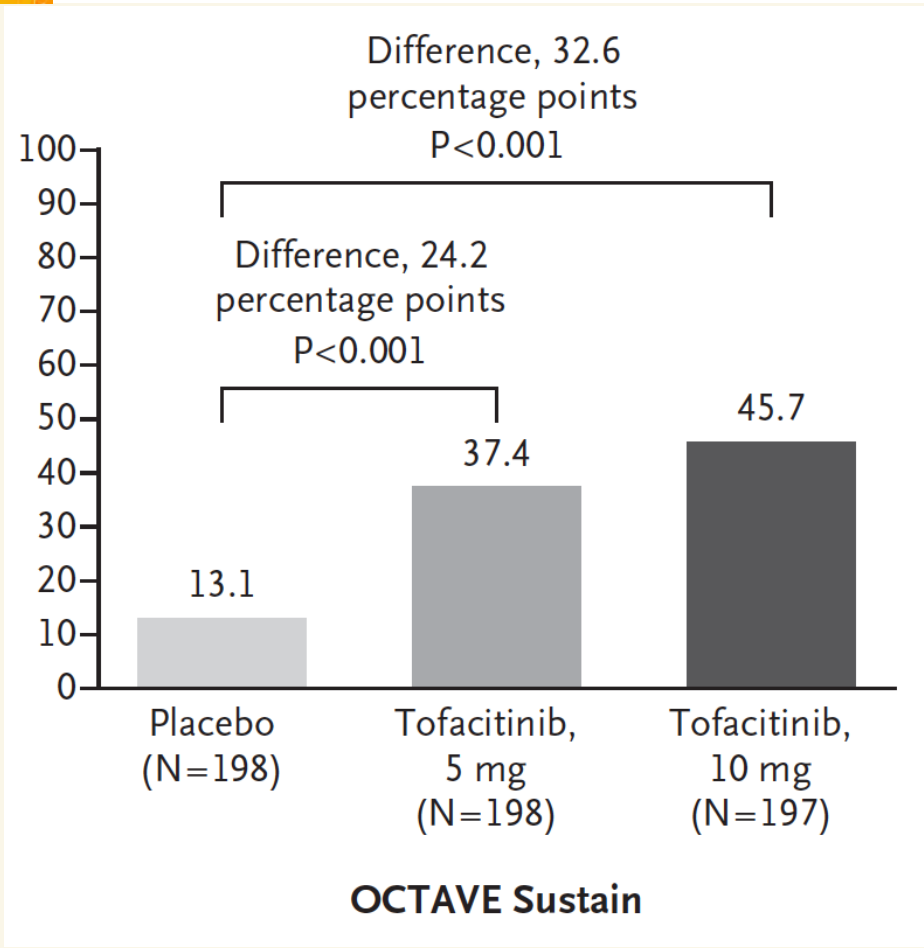
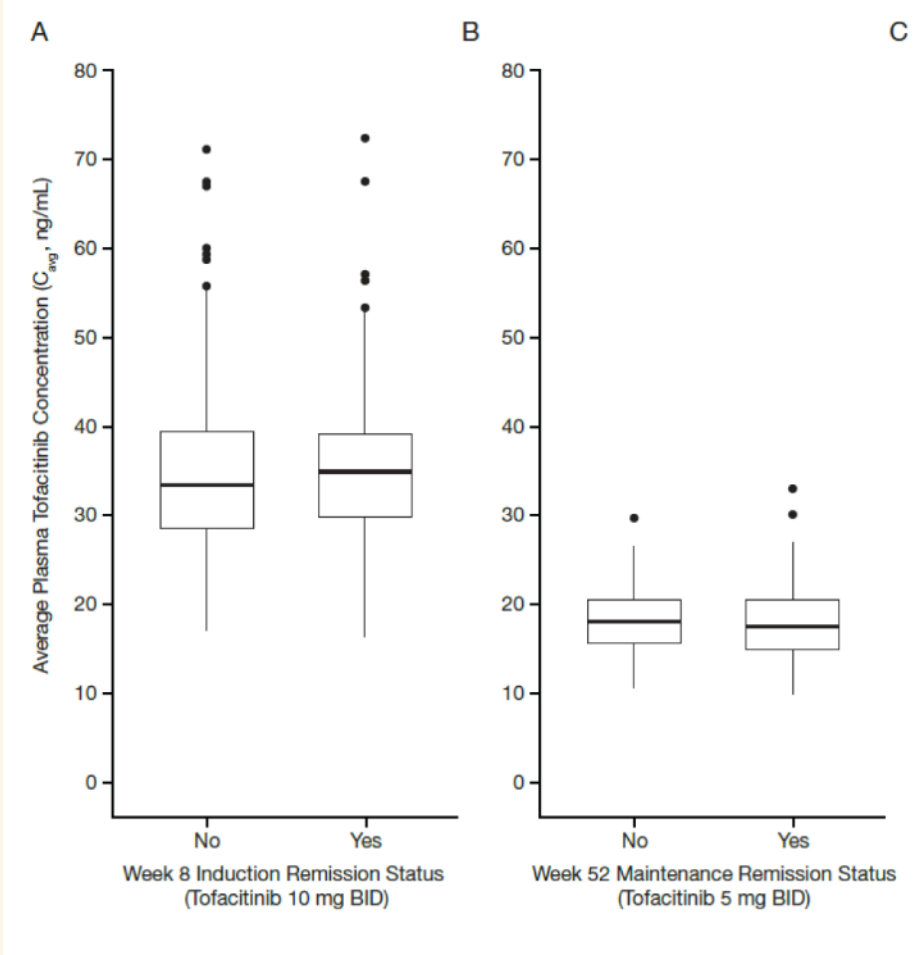
Tofacitinib Efficacy and PK in UC Phase 3 Clinical Trial

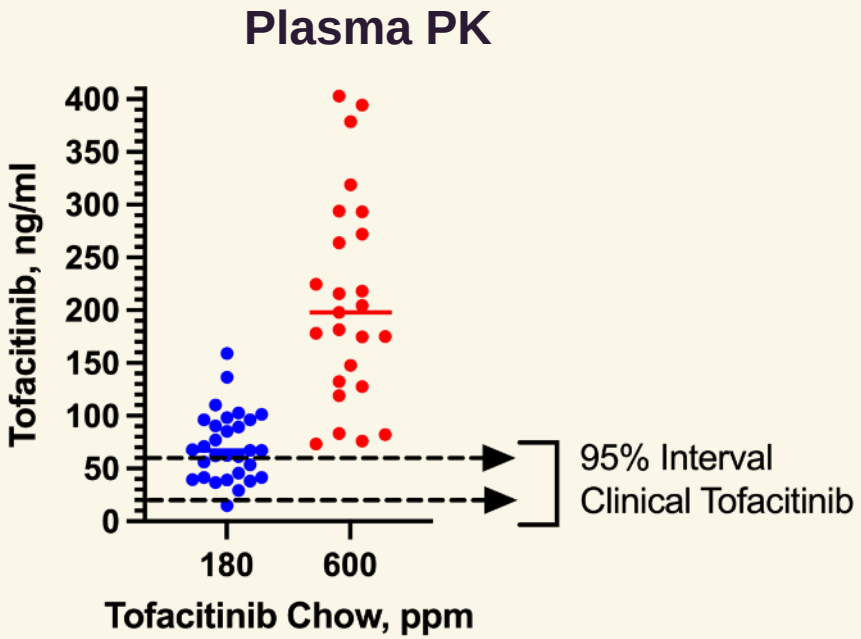


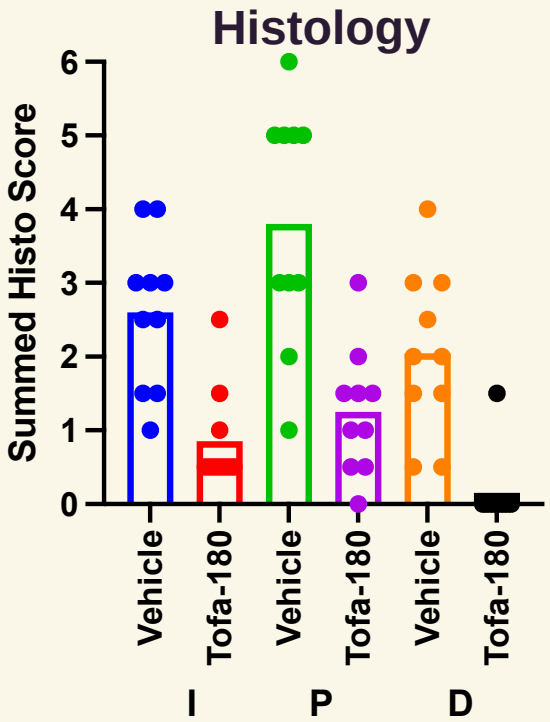


- **Left**: Mucosal healing after 52 weeks (remission data looks similar)
- **Right**: Average plasma exposure at 10 and 5 mg BID (**35 and 18 ng/ml**)
- *Note*: No PK differences as function of remission status

Sandborn WJ, et al. *N Engl J Med*. 2017 May 4;376(18):1723-1736.

Tofacitinib PK and Activity in TCT Mouse Model





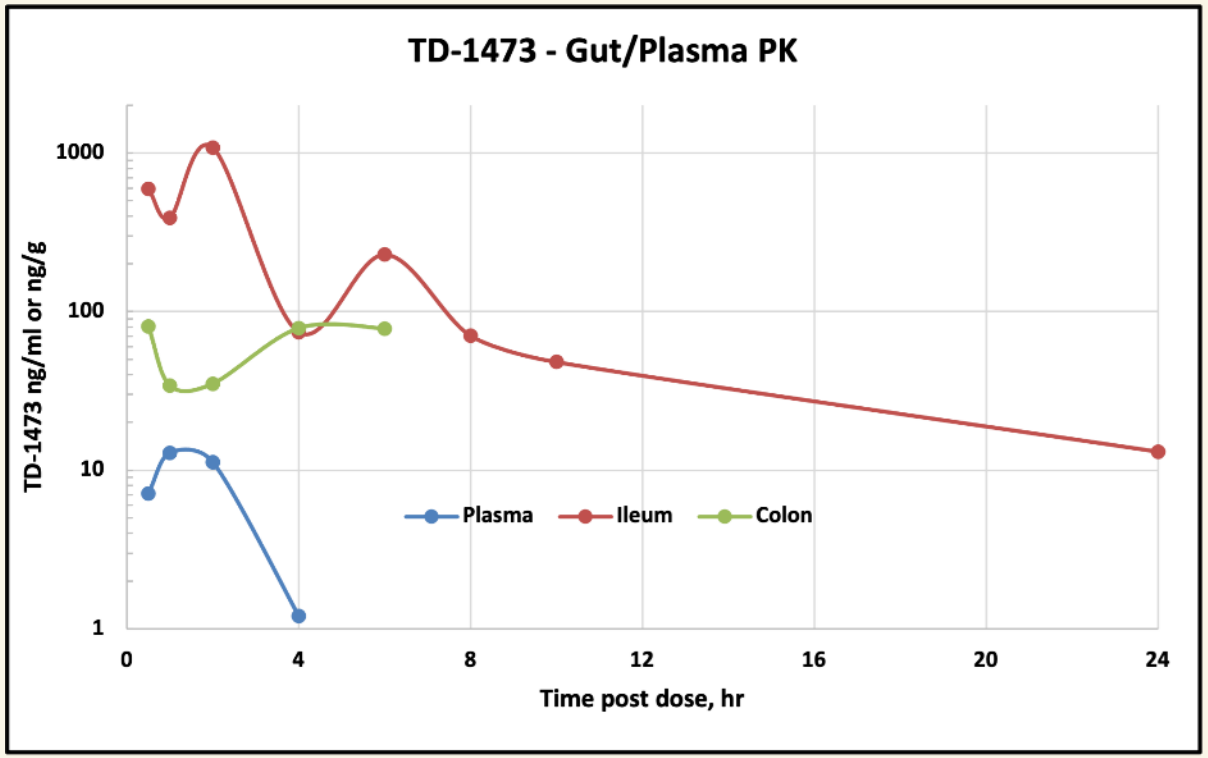
- **Left:** Tofacitinib plasma PK from all mouse TCT studies at 180 vs. 600 ppm chow – overlaid with dose range achieved clinically 10 mg BID (Phase 3[1])
- **Right:** At a dose of 180 ppm with chow dosing, tofacitinib achieved histological activity throughout GI (I – ileum, P proximal, D – distal colon)

Activity and dosing in Phase 3 *(PO BID)* and TCT mouse model *(chow)* are comparable and relevant for evaluation of our GB candidates

Data on file.

Theravance TD-1473: Gut-Selective JAK Inhibitor

TD-1473 Mouse PK



- Consistent with Theravance findings[1], after oral dosing in mice, TD-1473 achieved high concentrations in the ileum and colon, with low levels in the plasma[2]
- Dotted lines show levels of drug required to inhibit key cytokines in whole blood[2]
- **Hypothesis:** Limited plasma exposure should limit systemic effects
- **Unknown if high exposures in gut are - *by themselves* - sufficient to treat disease**

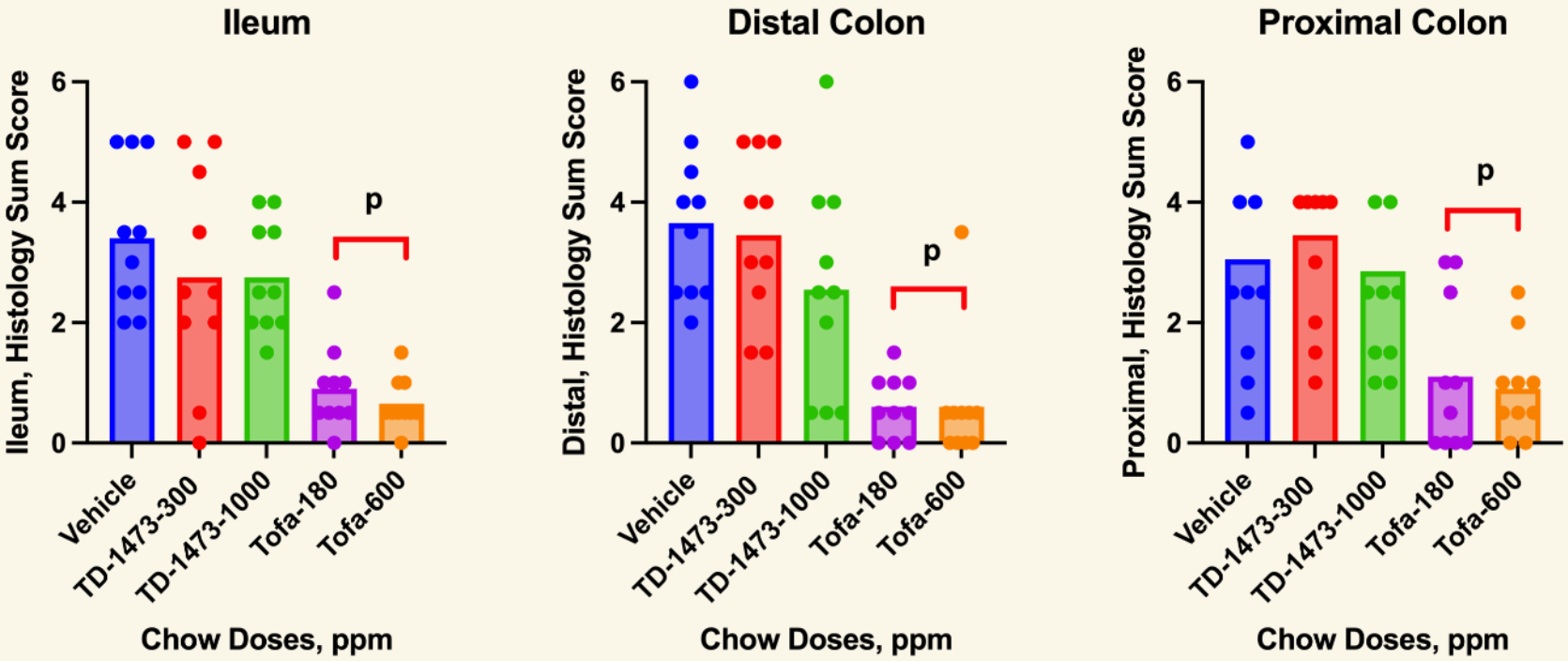
1. Sandborn WJ, et al. *J Crohns Colitis*. 2020 Sep 16;14(9):1202-1213.
2. Data on file.

TD-1473 TCT Mouse Model Data – In Life and *Ex Vivo*

- Unlike tofacitinib, TD-1473 at all doses failed to prevent weight loss during TCT studies – a predictor of efficacy
- Splenic CD4+ cells have significantly reduced levels of CD25 with tofacitinib dosing, but no change with TD-1473
- *Ex vivo* blood assay from study end showed only tofacitinib blocked IL-2 phospho-STAT5 in NK cells, no effect at any dose of TD-1473
- PK data from these studies consistent with low drug levels expected in mice with oral dosing

Data on file.

TD-1473 TCT Mouse Model Data - Histology



- Histological activity demonstrated in all tissues analyzed with tofacitinib
- TD-1473 did not demonstrate activity at any dose

Data on file.

Theravance TD-1473: Learnings from Aclaris Preclinical Studies

- Consistent with Theravance findings[1], TD-1473 primarily resides in the ileum > colon >> plasma[2]
- In life systemic activity measures (splenic CD4+ cell levels of CD25, *ex vivo* cytokine inhibition in whole blood) consistent with low plasma levels and lack of weight loss protection[2]
- No evidence of histological activity at any dose (100 – 1000 ppm) in any part of GI tract across two TCT studies[2]
- If TCT model is a better predictor of clinical efficacy, as opposed to the short-term oxazolone model used by Theravance, **these data may have predicted the failure of TD-1473 in Phase 2B UC**
- Subsequently, Theravance announced discontinuation of its Phase 2 study of TD-1473 for treating Crohn's disease[3]

1. Sandborn WJ, et al. *J Crohns Colitis*. 2020 Sep 16;14(9):1202-1213.
2. Data on file.
3. https://www.sec.gov/ix?doc=/Archives/edgar/data/0001583107/000110465921139570/tm2133032d1_8k.htm. Last accessed November 23, 2021.

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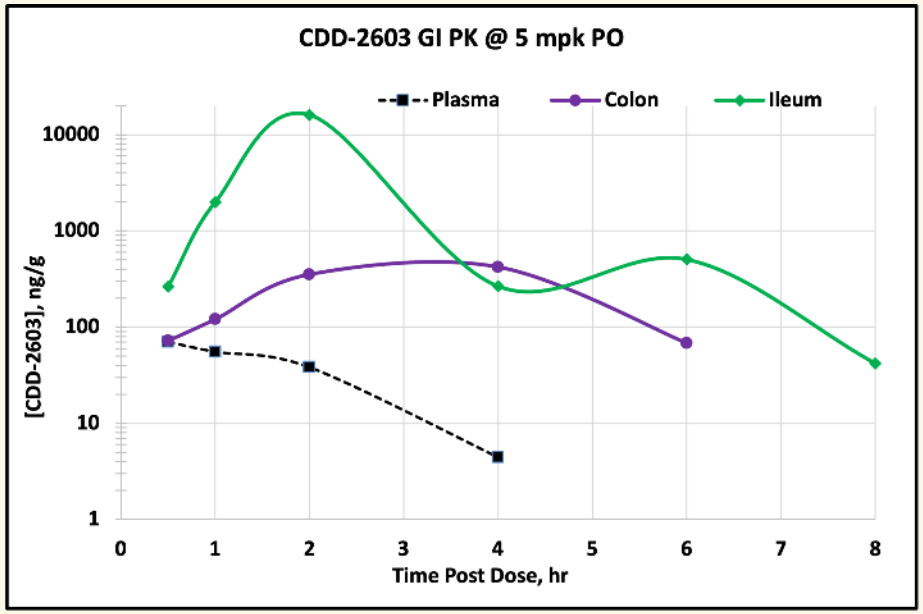
CDD-2603: Aclaris JAK GB Development Candidate

CDD-2603: A JAK GB Development Candidate

Mouse PK/Human PBMC Potency



	Human PBMC IC_{50}, nM	
	JAK1/3	Tyk2/JAK2
	IL-2	IL-12
CDD-2603	6	30
Tofacitinib	11	534

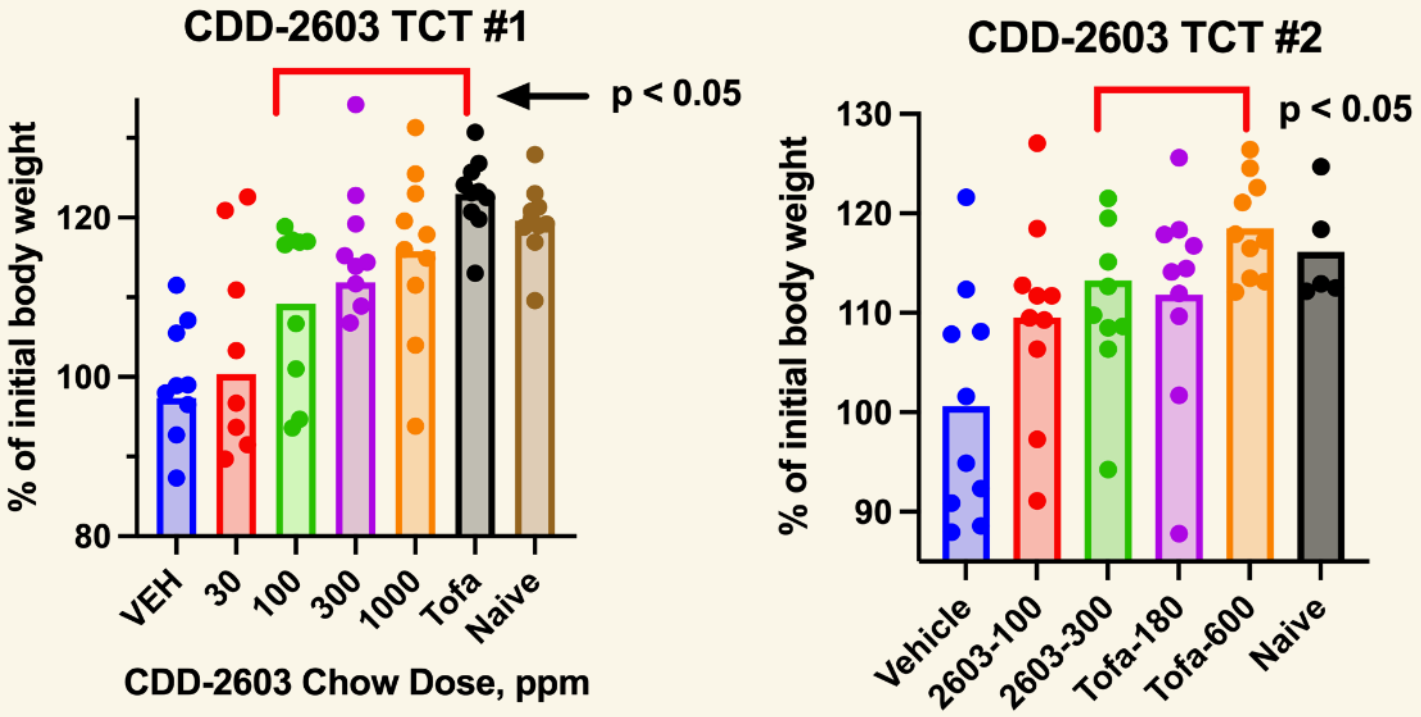
At all time points in mouse after dose of 5 mg/kg PO, drug concentrations in the **ileum and colon** are 50-500X higher than plasma

Table above compares CDD-2603 to tofacitinib in human PBMC assay of IL-2 and IL-12 induced P-STAT5/P-STAT4, respectively

Data confirmed that CDD-2603 is gut-biased in its distribution in mice (used for disease model activity) and potent in human PBMC

Data on file.

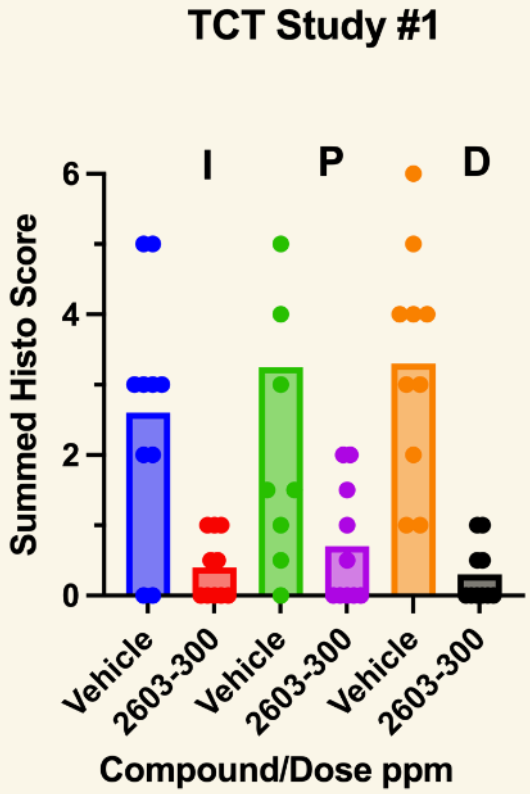
CDD-2603 TCT Mouse Model: Body Weight Changes

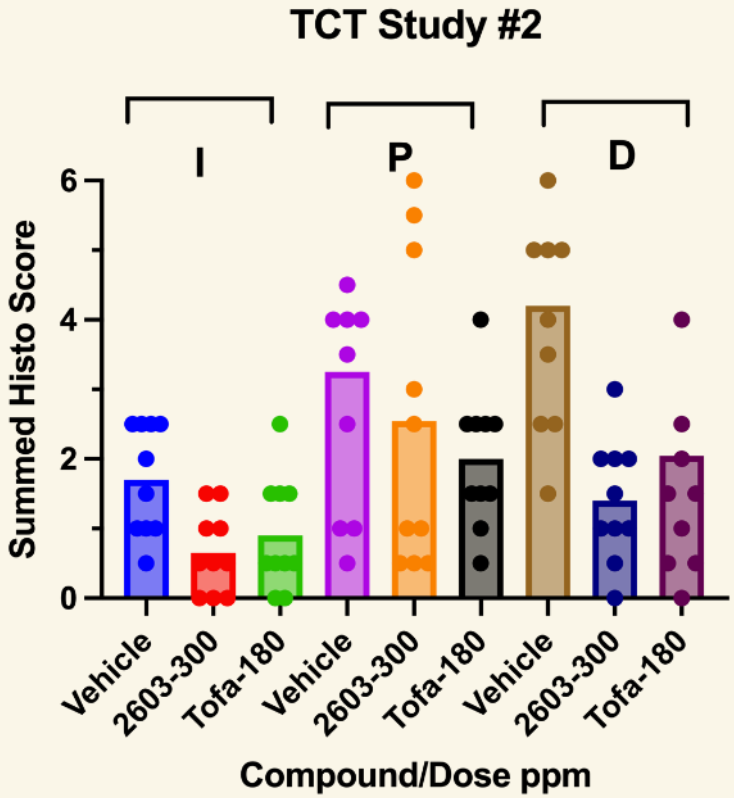


- In both TCT studies with CDD-2603, dosing begins on day 21, ends on day 49
- In life body weight changes showed improvement, down to 100 ppm dose

Data on file.

CDD-2603 TCT Mouse Model: Histological Activity

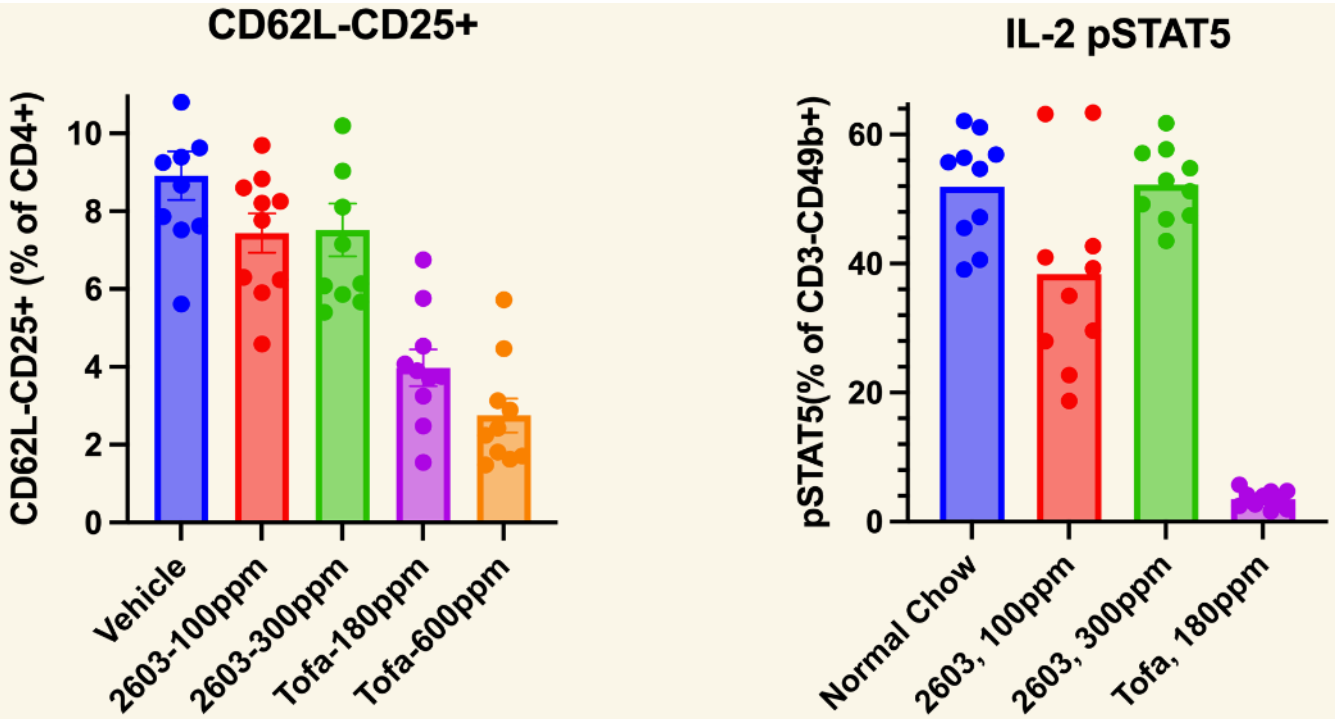




In repeat TCT studies, CDD-2603 produced histological activity in all regions of the colon and ileum at 300 ppm dose, comparable to tofacitinib

Data on file.

CDD-2603 TCT Mouse Model: Minimal Systemic Effects



- **Left:** Tofacitinib induced a dose dependent decrease in the percentage of splenocytes that are CD62L-CD25+; CDD-2603 had minimal effects on these cells (peripheral lymphoid organ)
- **Right:** Minimal effect of CDD-2603 on IL-2 *ex vivo* stimulated blood, whereas tofacitinib produced a significant decrease in pSTAT5 in NK cells (CD3-CD49b+)

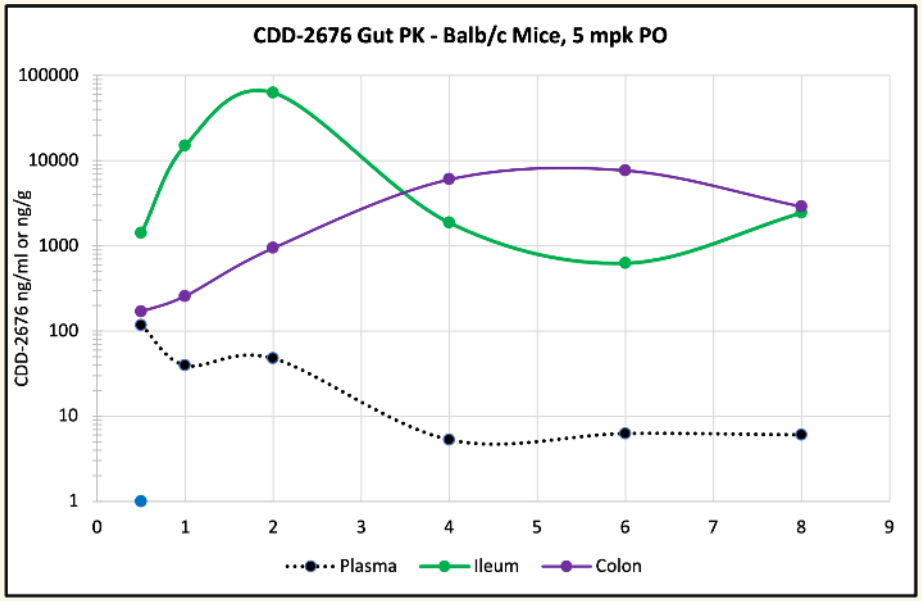
At doses that produced histological activity comparable to tofacitinib (as shown on previous slide), CDD-2603 demonstrated minimal systemic activity

Data on file.

CDD-2676: Aclaris JAK GB Development Candidate

CDD-2676: JAK GB Development Candidate

Mouse PK/Human PBMC Potency



	Human PBMC IC_{50}, nM	
	JAK1/3	Tyk2/JAK2
	IL-2	IL-12
CDD-2676	13	110
Tofacitinib	11	534

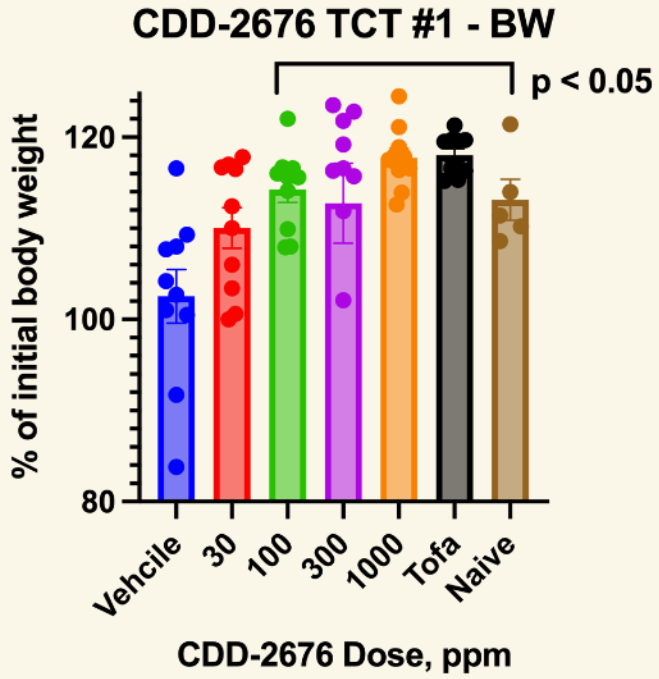
Plasma and intestinal PK of CDD-2676 in mice after 5 mg/kg PO dose show that drug levels in plasma do not reach the IL-2 IC50 for any period of time, whereas drug levels in colon and ileum are 100-1,000-fold higher

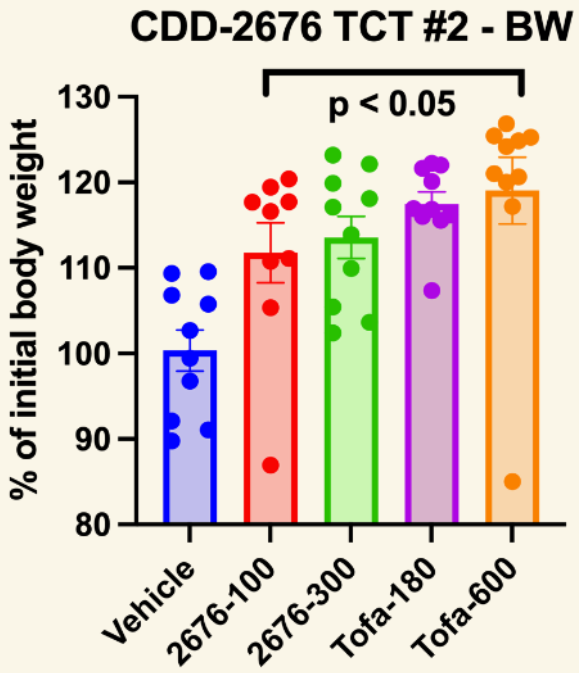
Table above compares CDD-2676 to tofacitinib in human PBMC assay of IL-2 and IL-12 induced P-STAT5/P-STAT4, respectively

Data confirmed that CDD-2676 is gut-biased in its distribution in mice (used for disease model activity) and potent in human PBMC

Data on file.

CDD-2676 TCT Mouse Model: Body Weight Changes

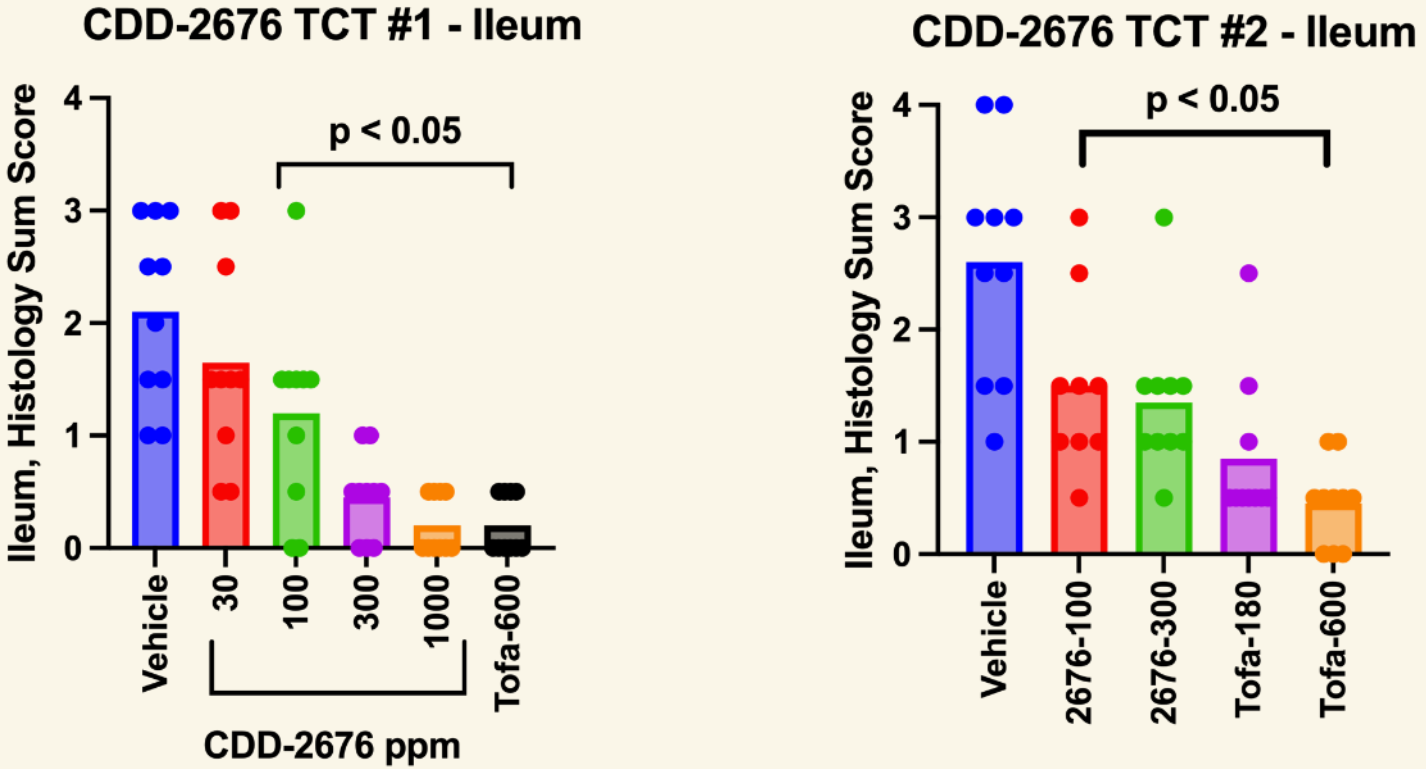




- In both TCT studies with CDD-2676, dosing begins on day 21, ends on day 49
- In life body weight changes showed dose-responsive effect, down to 100 ppm

Data on file.

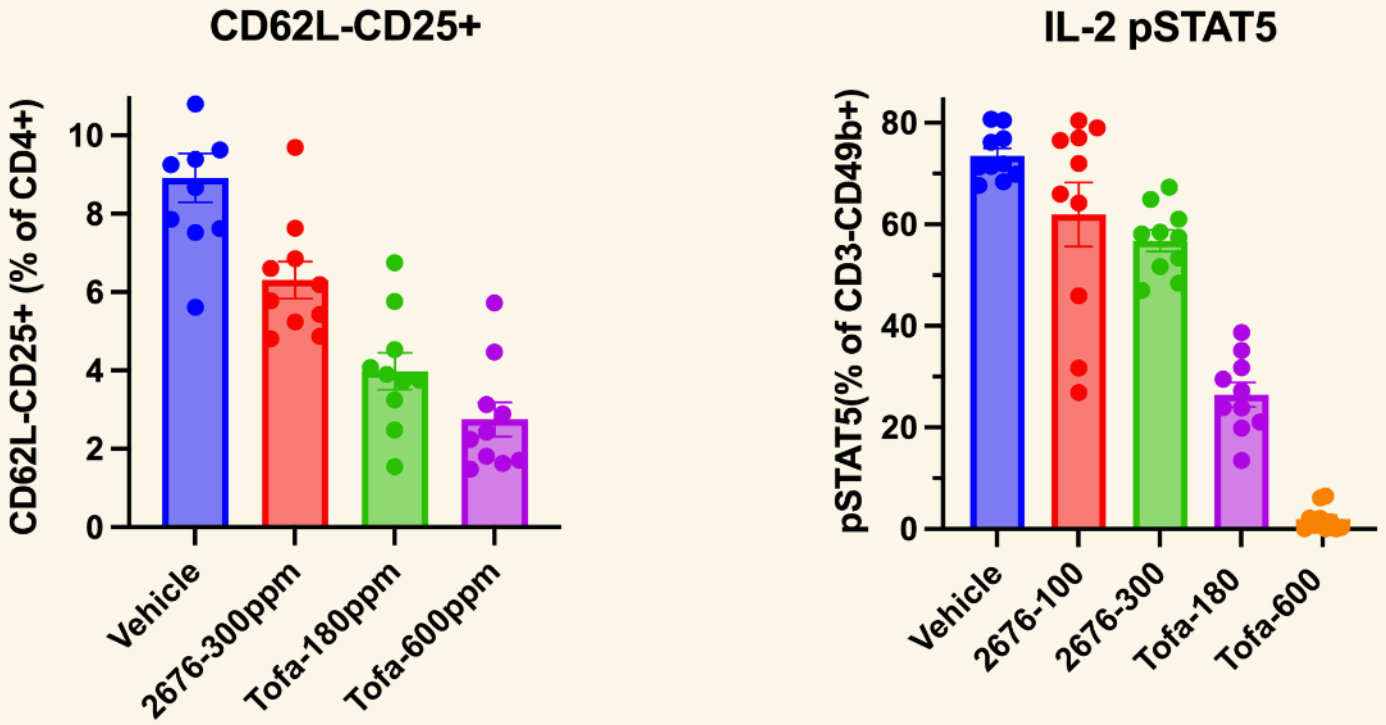
CDD-2676 TCT Mouse Model: Histological Activity



- In both TCT studies, CDD-2676 produced histological activity in the ileum down to 100 ppm (above) with variable activity in the colon down to 300 ppm
- ***Note:*** *Tofacitinib dosed at 600 ppm produced exposures much higher than those used clinically. Tofacitinib at 180 ppm (2nd study) is the only relevant comparator.*

Data on file.

CDD-2676 TCT Mouse Model: Minimal Systemic Effects



- **Left:** Tofa induces a dose dependent decrease in the percentage of splenocytes that are CD62L-CD25+, CDD-2676 has minimal effects on these cells (peripheral lymphoid organ)
- **Right:** Minimal effect of CDD-2603 on IL-2 *ex vivo* stimulated blood, whereas tofacitinib produced a dose-dependent significant decrease in pSTAT5 in NK cells (CD3-CD49b+)

At doses that produced histological activity comparable to tofacitinib (as shown on previous slide), CDD-2676 demonstrated minimal systemic activity

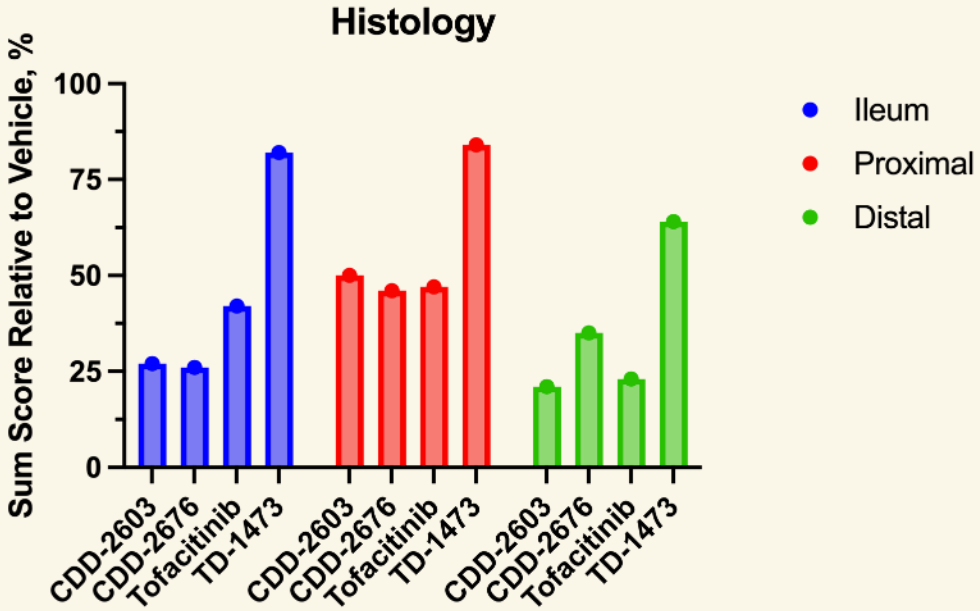
Data on file.

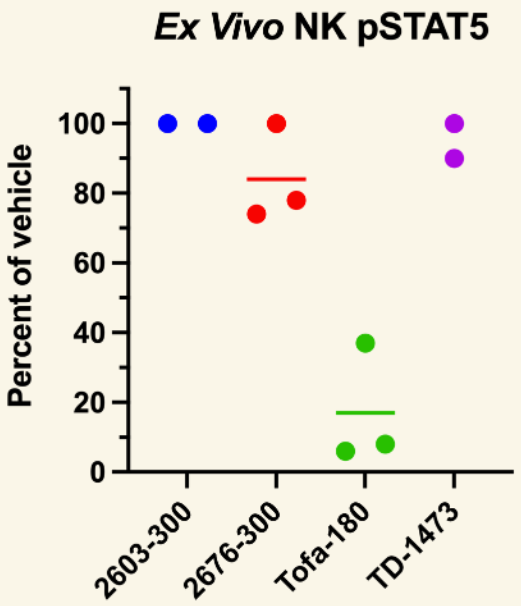
CDD-2603 and CDD-2676: 7 Day Rat Toxicology

- Both GB development candidates have completed 7 day dose-range finding study in rats at doses of 30, 100 and 300 mpk; no adverse events
- TK confirms gut-biased distribution in rats (similar to mouse)
- Decreased weight in lymphoid organs consistent with mechanism (e.g., thymus, spleen)
- Second tox species will be cynomolgus monkeys, given the known GI sensitivity to drugs in canine studies

Data on file.

Summation: Histological Activity vs. Systemic Activity in Mice





- Activity in IBD defined by histological improvement: **Reduced sum scores** = ***protection from tissue damage***
- Data across GI tract showed that CDD-2603 and CDD-2676 were comparable to tofacitinib, and TD-1473 was less active
- *Note*: Data is average of histological scores relative to vehicle across two studies for each compound

- Analysis of *ex vivo* stimulated whole blood from TCT studies is a measure of systemic effects
- Although comparable to tofacitinib histologically, CDD-2603 & CDD-2676 had less effect systemically
- Supportive data seen in analysis of splenic CD4 cell activation (blocked by tofacitinib)

Data on file.

Oral JAK GB Candidate – Summary and Plans

- Two JAK GB development candidates with histological activity in a murine IBD model comparable to tofacitinib have been identified
- Within the same TCT model, these development candidates also demonstrated fewer systemic effects within *ex vivo* blood assays and splenic CD4 cell activation compared to tofacitinib
- Toxicology studies (7 day rat) have been completed; histopathology data is being analyzed/generated
- Additional studies comparing CDD-2603 and CDD-2676 in normal mice with full complement of immune cells are underway, in an attempt to further distinguish between the two potential candidates

Data on file.

Closing Remarks and Q&A

R&D Day Key Takeaways

- Zunsemetinib
  - ✓ Phase 2 programs are on track
    - Three phase 2 studies planned in RA, HS, and PsA
  - ✓ Planning to add 2 programs
  - ✓ Recent preclinical work has demonstrated a dose-dependent inhibition of IL-17 production
- MK2 inhibitor use in oncology
  - ✓ Potential role for the MK2 pathway in:
    - Metastatic breast cancer
    - PDAC (Recent publication in Science Translational Medicine)
  - ✓ ATI-2231 – new MK2 inhibitor
- ATI-2138 – oral covalent inhibitor of ITJ
  - ✓ IND allowed
  - ✓ SAD studies to commence in 2021
- Gut-biased Development Candidates selected for IBD

Key Milestones

Program/Milestone	2021				2022			
	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q
Zunsemetinib (ATI-450): MK2 Inhibitor								
Phase 2a Data in Moderate to Severe Rheumatoid Arthritis	✓							
Initiate Phase 2b Trial in Moderate to Severe Rheumatoid Arthritis								
ATI-1777: Topical "Soft" JAK Inhibitor								
Phase 2a Data in Moderate to Severe Atopic Dermatitis		✓						
Initiate Phase 2b Trial in Moderate to Severe Atopic Dermatitis								
ATI-2138: ITK/TXK/JAK3 Inhibitor								
Submit IND				✓				
Initiate Phase 1 SAD Trial in Healthy Volunteers								
ATI-2231: MK2 Inhibitor								
Submit IND								

Question and Answer Session

- Co-founded Aclaris in 2012
- Board-certified dermatologist
- Serial entrepreneur with over 20 years of experience in the life sciences industry

Neal Walker
Co-founder, President & CEO, Director

- Former Executive Director, Pfizer Inflammation Research and Leader of Global Kinase Technology Team
- >95 publications and patents (>30 total on kinases)

Joseph Monahan, PhD
Chief Scientific Officer

- Immunologist/drug discovery leader at pharma (Pfizer & biotech)
- Validated JAK 1/3 as target for transplant/RA/psoriasis, leading to approval of XELJANZ®

Paul Changelian, PhD
VP, Biology

- Co-founded Aclaris in 2012
- Senior financial executive with more than 25 years of biotech and specialty pharmaceutical management expertise

Frank Ruffo
Chief Financial Officer

- Former VP Research & Global Head, Pfizer Inflammation, co-leader of Pfizer Licensing Team
- Delivered 8 clinical candidates, 6 INDs and 1 NDA in inflammation and cancer

Walter Smith
Scientific & BD Consultant