

EMPOWERING PATIENTS THROUGH  
**REVELATIONARY**  
SCIENCE

**Aclaris Therapeutics**  
**Research & Development Day**  
**September 27, 2019**



# 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 preclinical and clinical drug candidates, including the timing for initiation and completion of preclinical studies and clinical trials, and the availability of data from these studies and trials, and the timing of its regulatory submissions related to its clinical trials. 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, 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, 2018, Aclaris' Quarterly Report on Form 10-Q for the quarter ended June 30, 2019, 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" section of the Investors page 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. This data involves 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.

# Aclaris Strategy

- Divest our commercial and near-term commercial assets
- Shift from fully integrated dermatology company to development stage biotechnology company focused on immunology and inflammation
  - Leverage competitive differentiation in kinase development
    - World class leadership in ex-Pfizer kinase development team
    - Leaders in cysteinome-based targets
  - Focus on small molecule therapeutics
    - Efficient drug development with ability to develop oral, topical, or gut restricted dosage forms
  - Target novel therapeutics involving known pathways
    - Better predictability of pharmacodynamic effects and therapeutic window

# Market Opportunity and Positioning

- Market opportunity
  - Protein kinases comprise a major gene family within the human genome, consisting of approximately 500 proteins responsible for the selective phosphorylation of up to 30% of the genome.
    - Over 40 kinase inhibitors have been FDA approved for indications in oncology and chronic inflammation representing multi-billion dollar markets<sup>1</sup>
    - Marketed kinase inhibitor drugs target less than 5% of the human kinome.
    - Approximately 60% of the human kinome contains noncatalytic cysteine residues in various orientations around the ATP binding site. This subset of kinome is referred to as the “cysteinome”
- Positioning
  - **Leaders in systematic targeting of the cysteinome**
    - Specialized expertise in addressing cysteinome targets by:
      - Tuning KINect™ proprietary chemical library to include core kinase binding elements and chemical ‘warheads’ specifically designed to engage cysteinome targets reversibly and covalently.
      - Building unique capabilities required to evaluate reversible and covalent drug candidates.

# Overview of R&D day

- Key takeaways:
  - Strategic shift to inflammation
  - Leadership in kinase inhibitor development with a particular emphasis on the cysteinome
    - Dedicated to the design of innovative, kinase-targeted medicines
    - Novel kinase inhibitor in the clinic as well as in pre-IND advancement
    - Identification of substrate selective, kinase complex stabilizing drugs, tissue selective kinase inhibitors, and covalent inhibitors of cysteinome kinases
  - Differentiated drug discovery engine
    - KINect™ discovery platform confers a differentiated competitive advantage in speed, quality, and efficiency
  - Compounds targeting large market opportunities over next two years:
    - MK2 – novel target for a plethora of inflammatory indications
    - ITK/JAK3 – potential best in class covalent inhibitor
    - Topical soft JAK – potential best risk/benefit for patients with moderate to severe AD

# Market Overview of Select Inflammatory Indications

	RA (moderate - severe)	Psoriasis (moderate - severe)	Ulcerative Colitis (moderate - severe)	Crohn's (moderate - severe)	Atopic Dermatitis (moderate - severe)
<b>2018E WW Sales<sup>1</sup></b>	~25B	~15B	~\$5B	~\$11B	~\$1B
<b>Estimated Peak Market (WW)<sup>2</sup></b>	~\$25-30B	~\$20-25B	~\$8-12B	~\$15B	~\$8-12B
<b>Prevalent US Moderate/Severe Population<sup>3</sup></b>	~1,000K+	~1,000-1,300K	~400-500K	~350-450K	~300-700K
<b>Approved Agents (per target)</b>	TNF-alpha: 5	TNF-alpha: 3	TNF-alpha: 2	TNF-alpha: 3	IgE: 1
	CD20: 1	IL-12 / IL-23: 2	Integrin $\alpha 4\beta 7$ : 1	IL-12 / IL-23: 1	IL-5: 3
	JAK: 2	IL-17A: 2	JAK: 1	Integrin $\alpha 4\beta 7$ : 1	IL-4R: 1
	Integrin $\alpha 4\beta 7$ : 1	PDE4: 1			
	Other: 3				
<b>Agents in Clinic (per target)</b>	BTK: 9	IL-23: 2	JAK/STAT: 4	JAK/STAT: 5	IL-33: 4
	JAK/STAT: 5	IL-17 / IL17R: 4	IL-23: 4	IL-23: 5	DP2 R: 2
	IL-6: 3	JAK/STAT: 2	S1P-R: 2	S1P Receptor: 3	TSLP: 1
	TNF-alpha: 1	Others: 7	Integrins: 2	Integrin $\alpha 4\beta 7$ : 1	IL-4R: 1
	T-cell Receptor: 1		Others: 12	Others: 12	IL-5: 1
	Others: 41				Others: 6
<b>Opportunity for New Treatments</b>	Orals, Improved risk/benefit, novel mechanism	Oral, novel mechanism, improved safety	Gut-restricted (improved safety)	Gut-restricted (Improved safety)	Improved risk/benefit, topical in moderate to severe

\*Auster M., et al. Something Big Is Getting Bigger [research note]. New York, NY: Credit Suisse Equity Research; 2019.

(1) Estimates of total sales per indication from EvaluatePharma

(2) CS projections: based on US branded pricing

(3) Assumed peak treatable population with population with population with biologics/novel agents in the US: R 350-400k / Psoriasis 300-350k / Ulcerative Colitis 225-275k / Atopic Dermatitis 150-200k / Asthma 275-325k

# Atopic Dermatitis Market Opportunity

- Atopic dermatitis (AD) is a disease of unknown origin that usually starts in early infancy and is typified by pruritus, eczematous lesions, xerosis (dry skin), and lichenification on the skin (thickening of the skin and increase in skin markings).
  - Rates of AD are around 30% in the most developed nations and exceed 10% in many countries<sup>1</sup>
  - Worldwide cumulative prevalence of 15-20%<sup>1</sup>
  - Topical steroids work well for a large percentage of AD patients; however, up to 50% of those with moderate and 80% of those with severe disease will fail long-term maintenance therapy.
- Large and growing market –
  - Projected to be \$8-12 billion at peak (moderate to severe AD)<sup>2</sup>
  - Projected to be ~\$4.5 billion in 2024<sup>3</sup>
- Recently approved therapies:
  - EUCRISA (crisaborole) – mild to moderate
  - DUPIXENT (dupilumab) – moderate to severe
- Unmet need for novel therapies, delivery methods, and regimens given dearth of safe and effective options suitable for long-term chronic use.
  - Emollient-containing solution – convenience
  - Soft drug approach
  - Moderate to severe atopic dermatitis
    - Monotherapy
    - Adjunctive therapy

<sup>1</sup> James W, et al Andrew's Diseases of the Skin Clinical Dermatology, 2011, 11<sup>th</sup> edition

<sup>2</sup> Auster M., et al. Something Big Is Getting Bigger [research note]. New York, NY: Credit Suisse Equity Research; 2019.

<sup>3</sup> Therapeutic Categories Outlook - Cowen and Company, March 2019



# Inflammation Market Opportunity

## *MK2 inhibitor and ITK/JAK3*

- Inflammatory/autoimmune markets have grown significantly in recent years
- US Market size of ~\$54 billion in 2018 - driven by biologics<sup>1</sup>
  - In the US the number of patients with autoimmune diseases being treated per year is up 63% since 2013<sup>2</sup>
  - Although crowded and competitive, very attractive field due to breadth of indications, heterogeneity, multiple entry points, common practice of cycling through therapies and continued unmet need in many patient subsets
  - Route of administration is a significant factor in the under-penetration of biologics - has implications on acceptance, compliance and overall cost to the healthcare system.
- Need for additional oral therapies:
  - Patients/Physicians are receptive to oral therapies which are nearly as efficacious as biologics, well tolerated, and convenient to administer as they provide another option for anti-TNF therapies failures
  - Therapies with a novel mechanism of action could be readily adopted by patients who often have the bias of oral medications being safer than injectables and over time oral medications could come earlier in treatment algorithms before biologics.
  - While superior dosing convenience and efficacy is the best-case scenario (i.e. XELJANZ in RA), dosing convenience alone without differentiation on efficacy can be enough (i.e. OTEZLA in psoriasis)
- OTEZLA (apremilast) case study:
  - Approved in psoriatic arthritis Mar 2014 and moderate-to-severe plaque psoriasis 9/14; approved for both indications in EU in 1/15.
  - Annual sales of \$472M, \$1.02B, \$1.28B, \$1.61B, from 2015-2018 respectively. Acquired by AMGN for \$13.4B<sup>3</sup>
  - Safety Profile (and lack of monitoring) have enabled it to be used in two relatively new settings:
    - as an adjunctive therapy on top of high efficacy biologics and
    - as a monotherapy in mild-moderate psoriasis

<sup>1</sup> IQVIA - the-global-use-of-medicine-in-2019-and-outlook-to-2023 – pg48

<sup>2</sup> 5-19 - IQVIA -Medicine Use and pending in the U.S. A Review of 2018 and Outlook to 2023 - pg13

<sup>3</sup> Factset Drug sales data



# Inflammation Market Opportunity

## *MK2 inhibitor and ITK/JAK3*

- Many opportunities exist for novel agents to gain share:
  - Cycling through different therapies/medications is common.
  - Efficacy of biologics in the treatment of inflammatory / autoimmune disease can fade over time due to:
    - Development of anti-drug antibodies
    - Recalcitrant disease
    - Suboptimal dosing regimens
  - A large proportion of patients do not achieve long-term responses with currently available options and while physicians may switch to a therapy in the same class, switching to agents with different/novel mechanism is preferable when there is data which suggests for better outcomes with the new MOAs.
  - Demonstrated efficacy in an autoimmune disease may indicate utility in related diseases.
- MK2 inhibitor:
  - RA market of \$25 billion in 2018<sup>1</sup>
  - Oral therapy
- ITK/JAK3:
  - Psoriasis market of \$15 billion in 2018<sup>1</sup>
  - Oral therapy

# Inflammation Market Opportunity

## *Gut Restricted ITK and/or JAK Inhibitors as Drugs for Inflammatory Bowel Disease*

- Market opportunity<sup>1</sup>:
  - Including Crohn's disease and ulcerative colitis, there are an estimated 1.7 million people in the US with IBD
  - Increased by 200,000 since 2011
  - 70,000 new cases are diagnosed each year.
  - There may be as many as 80,000 children in the US with IBD.
  - Worldwide, IBD is estimated to affect close to 5 million people.
  - Estimated 2018 global sales for UC and CD were ~\$4.9B and \$11.4B respectively
- A study found that ~90% of UC/CD patients experience at least one indicator of suboptimal biologic therapy (dose escalation, discontinuation, switching, among others) within 36 months of biologic tx initiation.<sup>2</sup>
- 24-month discontinuation rates were > than 50% for both UC/CD, with a 10% and 14% rate of switching for UC and CD respectively for the same period.<sup>3</sup>
- Market need for Gut restricted options:
  - Targeted therapy with favorable risk/benefit profile

1 Therapeutic Categories Outlook - Cowen and Company, March 2019

2 Patel, Haridarshan, Trevor Lissos, and David T. Rubin. PloS one (2017)

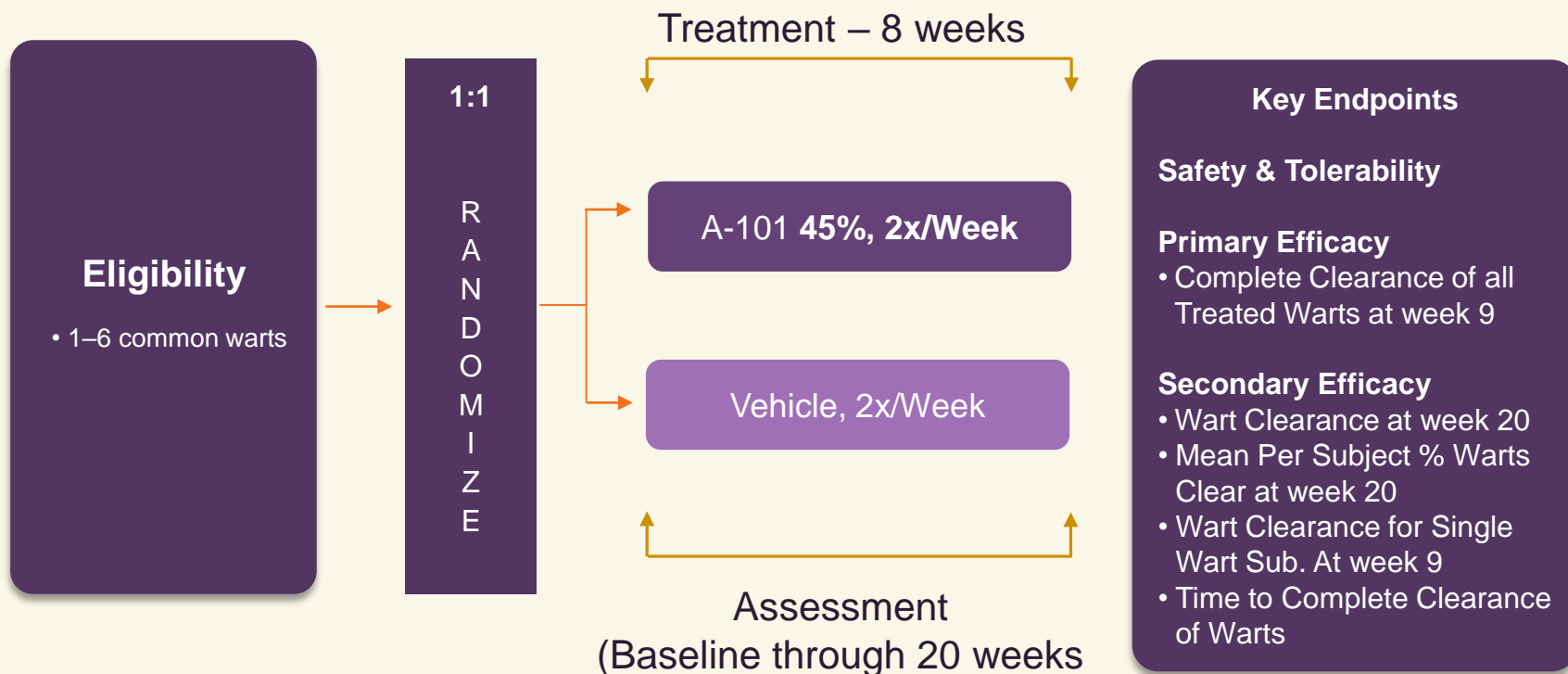
3 Null, Kyle D., et al. Value in Health (2017) -Ulcerative Colitis Treatment Patterns and Cost of Care

# Pipeline: New Focus

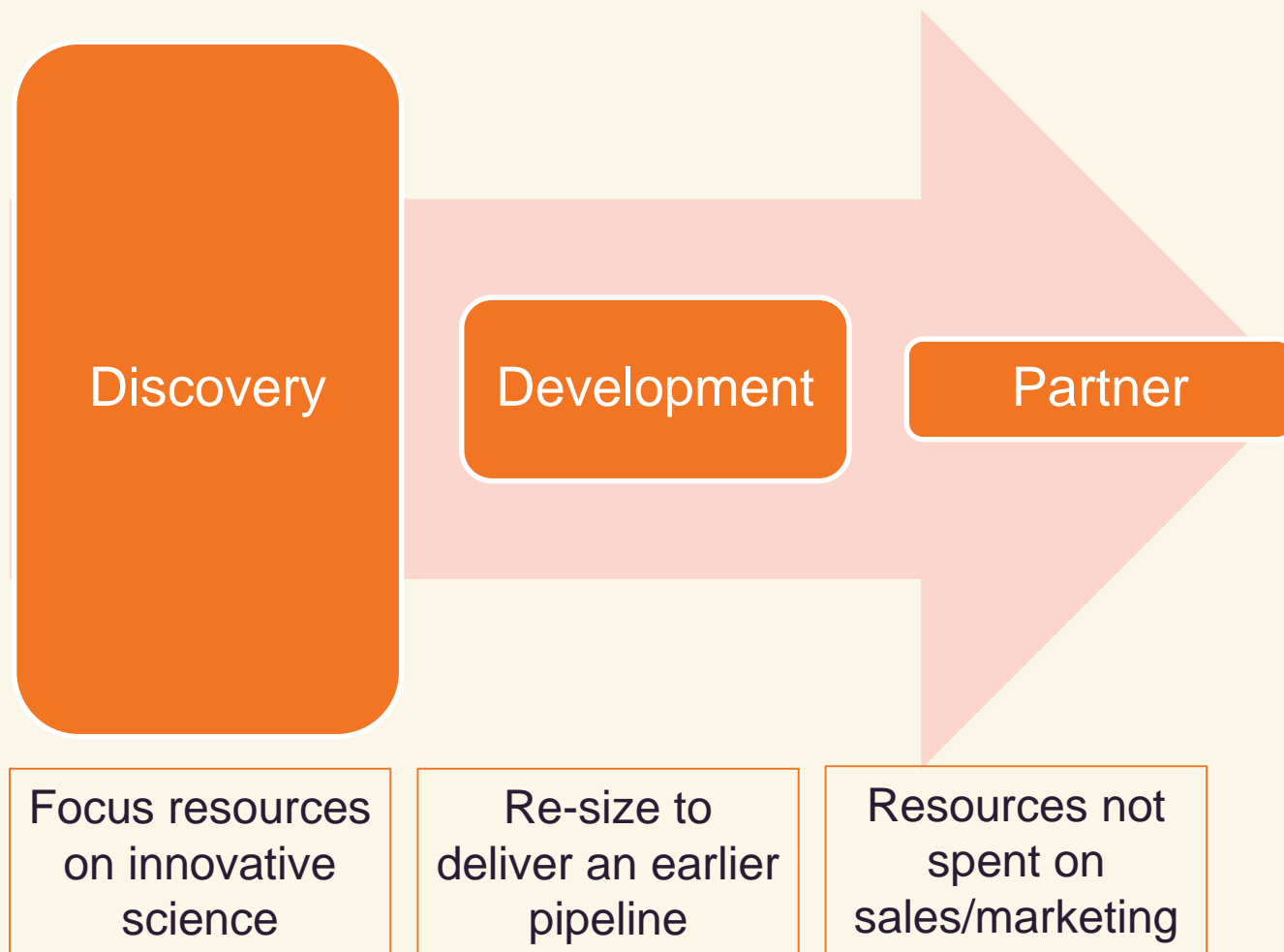
Program	Indication(s)	Preclinical	Phase 1	Phase 2	Phase 3
A-101(45%) <i>Topical</i>	Common Warts				
ATI-450 MK2 Pathway Inhibitor <i>Oral</i>	RA, Psoriasis				
ATI-1777 JAK1/JAK3 Inhibitor <i>Soft Topical</i>	Atopic dermatitis				
ATI-2138 ITK/TXK/JAK3 Inhibitor <i>Oral</i>	Psoriasis, Inflammatory Dermatoses				
ITK/JAK3 Inhibitor <i>Oral, gut-restricted</i>					
MK2 Pathway Inhibitor <i>Oral</i>					
	Ulcerative colitis / Crohn's Disease				
	Oncology				

# THWART 1&2 : A-101 45% Topical Solution Hydrogen Peroxide (an investigational compound) compared to Vehicle in Subjects With Common Warts

## Randomized, Double-blind, Vehicle-controlled Multicenter Study



# Business Model



# Discovery Leaders

## **Walter Smith** *SVP, R&D*

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

## **Joseph Monahan, PhD** *Exec. VP R&D* *(Head of Discovery)*

Former Executive Director, Pfizer Inflammation Research and Leader of Global Kinase Technology Team

>95 publications and patents (>30 total on kinases)

## **Jon Jacobsen, PhD** *VP, Chemistry*

Former Research Fellow and Director, Pfizer Chemistry  
>100 publications and patents (15 total on kinases)

Project Lead for PFE JAK Program

## **Paul Changelian, PhD** *VP, Biology*

Immunologist/drug discovery leader at pharma (Pfizer) & biotech (Lycera, Infinity)

Validated JAK 1/3 as target for transplant/RA/psoriasis, leading to approval of Xeljanz®

## **David R Anderson, PhD** *Sr. Director, Discovery and Early Development*

Former research project leader at Pfizer. Director of Chemistry at Mnemosyne, Luc, Cadent.

Inventor of 6 clinical candidates and author of 40 peer reviewed publications and patents

## **Gary DeCrescenzo** *SVP, Pharm Dev*

Former Exec. Director, Pfizer. Site Head for Medicinal & Structural Chemistry.

>100 patents.  
Co-inventor of multiple drug candidates

# Catalysts

Milestone	2019		2020			
	Q3	Q4	Q1	Q2	Q3	Q4
A-101 45% Common Warts						
Phase 3 Data (Thwart-1, Thwart-2)	✓					
Inflammation / Immunology						
ATI-450 (MK2 Inhibitor) - Initiate Phase 1 Trial (SAD/MAD)	✓					
ATI-450 (MK2 Inhibitor) - Phase 1 Data (SAD/MAD)						
ATI-450 (MK2 Inhibitor) - Initiate Phase 2 Trial in Rheumatoid Arthritis						
ATI-450 (MK2 Inhibitor) - Phase 2 data in RA						
ATI-1777 (Soft JAK) – Submit IND						
ATI-1777 (Soft JAK) – Initiate Phase 1 Trial						
ATI-2138 (ITK/JAK3) – Submit IND						



# Agenda

Introduction	Neal Walker David Gordon
KINect™ Platform	Joe Monahan
ATI-450: MK2 inhibitor	Walter Smith Paul Changelian
BREAK	
ATI-1777: Soft JAK inhibitor	Paul Changelian
ATI-2138: ITK/JAK3 inhibitor	David R Anderson
Gut restricted JAK and ITK/JAK inhibitors	Jon Jacobsen
LUNCH	

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## The KINect™ Platform: Our Drug Discovery Engine



# Technology Platform

# The Kinase Opportunity and Challenge

## Creating New Medicines Targeting Previously Inaccessible Kinome Targets

### Medically Important and Productive Target Class

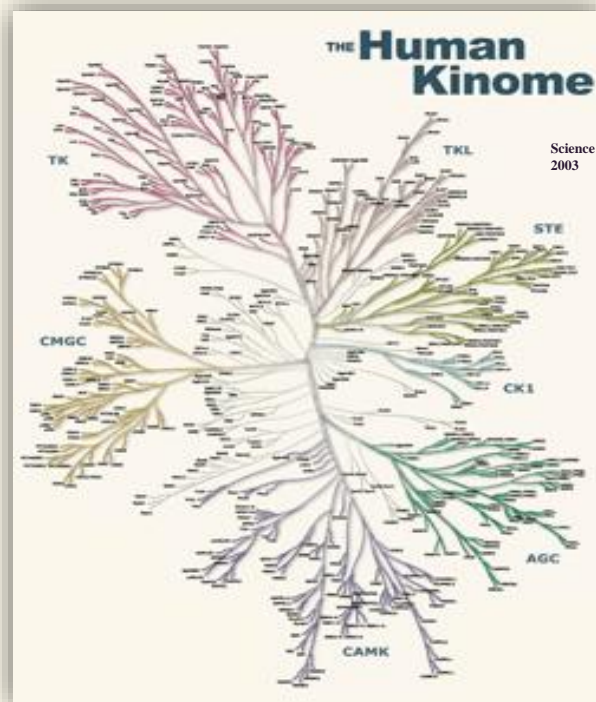


~36 Marketed Drugs

~\$48B\*

Annual Sales of Kinase Drugs

### Most Members of the Kinome Remain Unexplored



518 Members

>90% of the Human Kinome  
remains undrugged

Despite successes kinase drug discovery remains challenging

# The Aclaris Solution: The KINect™ Technology Platform

- Experienced and accomplished kinase drug discovery and development team
- Demonstrated success in generating clinical candidates for difficult to drug kinases with novel approaches
  - reversible and covalent inhibitors
- A portfolio of high interest targets with wide applications in immuno-inflammatory diseases
- Platform technology that has delivered on our current portfolio and will continue to develop new assets
- The ability to systematically and efficiently attack the human cysteinome differentiates Aclaris from competitors

# Confluence Discovery Technologies

*Experienced, Successful Drug Discovery and Development Team*

- 
- Target Validation
  - Structure Based Design
  - Medicinal Chemistry
  - Testing Funnel Design
  - Compound Screening
  - Lead Identification
  - Compound Mechanism of Action Studies
  - Disease Specific Cell Assays
  - Immunology Cell Assays
  - Biomarker Assays
  - In vivo Pharmacology
  - Development Candidate ID
  - PK, CMC and Safety
  - IND Submission
  - FIH

**State of the Art Laboratories, Technology and Experienced Drug Hunters**

- Extensive experience and success in kinase drug discovery
- Fully integrated team enables high quality and efficient execution



# KINect™ Platform

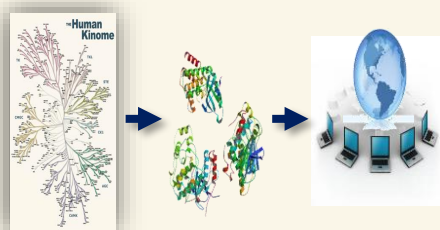
## Developing Kinase Drug Candidates Rapidly & Efficiently

TARGET SELECTION & VALIDATION

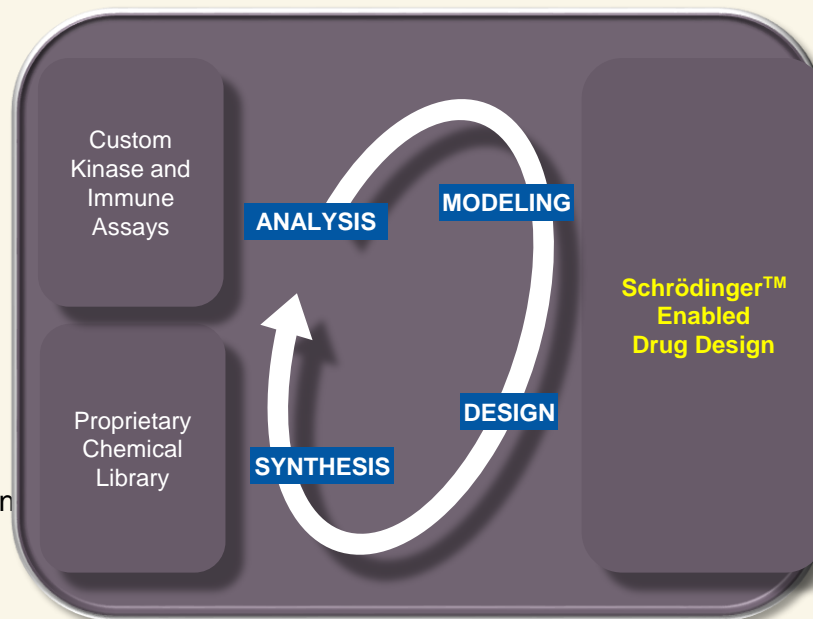
KINect™ Platform – LEAD GENERATION

ASSET GENERATION

500+ Kinases      Select Cysteine Kinases      Assess Target Confidence



>300 Cysteine Kinases      w/Published Crystal Structures      • Disease  
• Genetics  
• Safety  
• Distribution



Proprietary Portfolio

- MK2 Inhibitor
- JAK Inhibitors
- ITK Inhibitors

Strategic Partner(s)

- Project 1
- Project 2
- Project 3

- Leveraging key opinion leaders, data in public domain and internal validation

- Multiple approaches for difficult to drug kinases
- Fully integrated drug discovery team
- High affinity/selective drug scaffolds in proprietary library
- Faster path to lead optimization

- Demonstrated success with internal programs using multiple strategies



# KINect™ Platform Demonstrated Success

## *Reversible and Covalent*

### MK2 Pathway Inhibitor

#### Unique Substrate Selective Drug Design

- Oral anti-TNF, anti-IL-1, and IL-6 MK2 kinase inhibitor drug
- Novel solution for a difficult to target kinase
- ATI-450 (an investigational compound) currently in Phase 1 clinical study

### Tissue Restricted JAK Inhibitors

#### Tailoring physico-chemical and potency properties

- Potential efficacy with improved safety
- Project A: Soft, topical drug for the treatment of AD
- ATI-1777 (an investigational compound)
- Project B: Gut restricted inhibitor for Ulcerative Colitis and Crohn's

### Covalent ITK Inhibitors

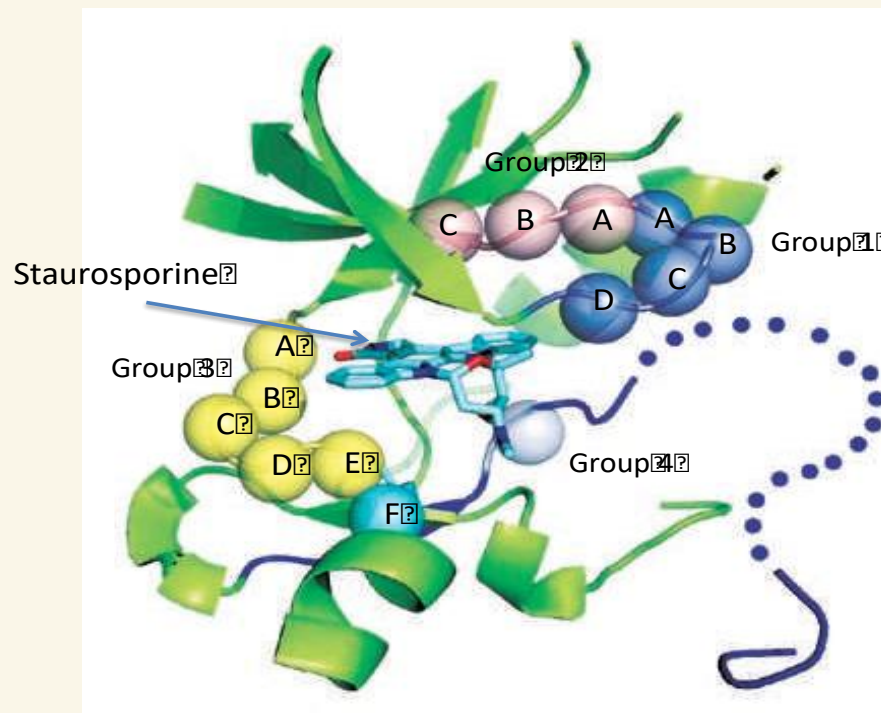
#### Covalent Inhibition: Solution for difficult to target kinase

- ITK T cell kinase inhibitors for autoimmune disease
- Reversible inhibition largely unsuccessful
- Oral and topical covalent drug candidates developed
- Oral: ATI-2138 IND enabling

# KINect™ Technology Platform

*Covalent inhibitors exploit the cysteinome to gain selectivity and potency*

## ***Utility of a Novel Thiol-Directed Chemical Library Coupled with Structure-Based Drug Design in Kinase Drug Discovery***

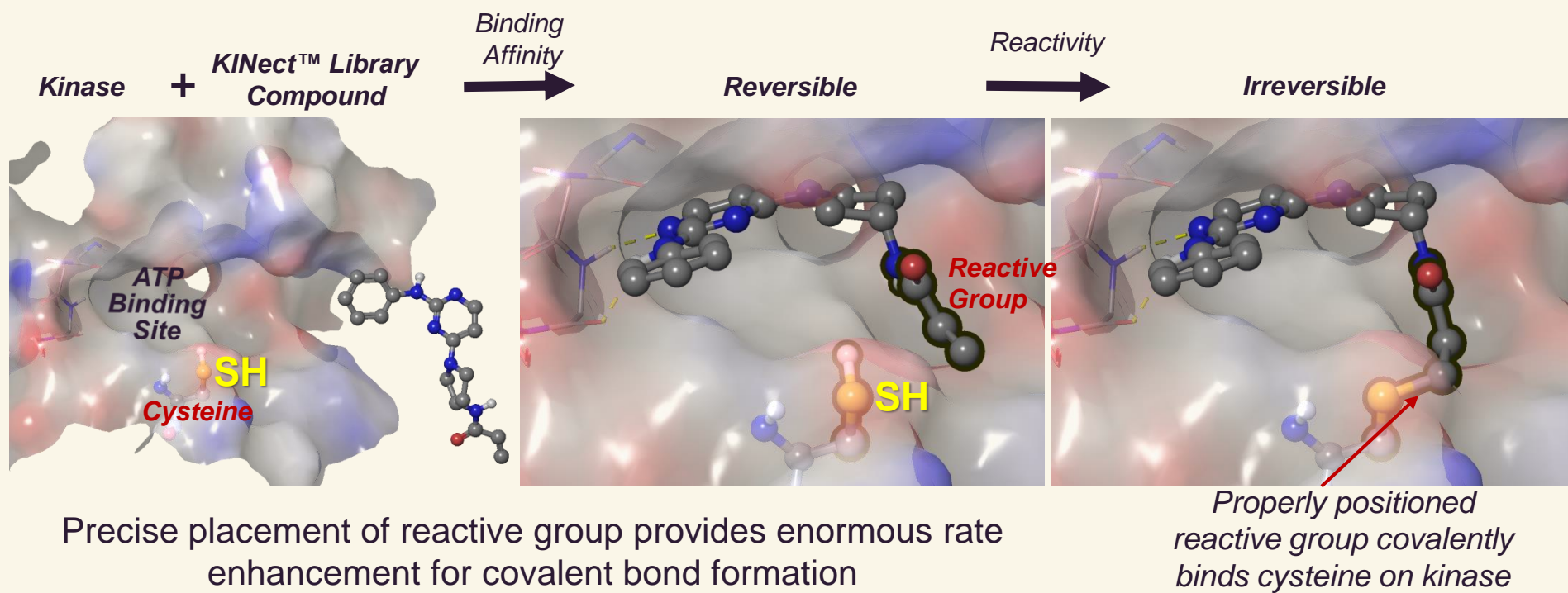


Groups 1-4 Grey, et. al., Nat. Rev. Cancer (2009)  
Group 5 T. Barf, et. al., J. Med. Chem. (2012)

- Covalent approach designed to address key issues in kinase drug discovery:
    - Biochemical efficiency
    - Kinome selectivity
    - Target potency
  - Multiple covalent kinase inhibitors approved by the FDA
  - **KINect™ Platform decreases time from target identification to lead optimization: Demonstrated for JAK and ITK programs**
- 313 of the 518 human protein kinases contain a cysteine near the active site
  - Covalent drugs target these cysteine residues

# KINect™ Technology Platform

## *Discovery of covalent kinase inhibitors*



**Maximizing** reversible affinity and **Minimizing** reactivity with the intent to develop efficacious and safe drugs

# KINect™ Platform

## *Novel library coupled with industry-leading expertise*

- KINect™ proprietary compound library
  - Purposely designed physical library of kinase scaffolds with electrophilic substituents
  - Library has been validated by generating lead optimization starting points
- Characterization of covalent binding
  - Use shift in  $IC_{50}$  with and without pre-incubation
  - Crystal structure confirmation
- Determination of  $k_{inact}/K_i$  to access true potency of inhibitors
  - $IC_{50}$  can benchmark activity but can be misleading
  - $K_i$  and  $k_{inact}$  can have separate structure activity relationship (SAR), important to evaluate both to drive project
  - Evaluate kinetics using progress curve analysis and global fitting
- Biochemical assays to address stability and reactivity of covalent inhibitors
- Cellular washout assays to confirm extended duration of action
- Cellular and *in vivo* determination of target occupancy
  - Clickable covalent probes

# KINect Library Validation

## Rapid Lead Identification for 10 Kinases of Interest

- Validation with 10 kinase targets chosen for structural diversity & disease biology (8 shown here)
- Lead chemical matter generated on all 10 targets in <2 months as lead optimization starting point
- Time dependent inhibition consistent with covalent binding
- Successfully delivered a development candidate for the ITK program

cysteine	3	3	3	4	4	2b	2b	3b		cysteine	3	3	3	4	4	2b	2b	3b	
Corporate ID	KIN 1	KIN 2	KIN 7	KIN 8	KIN 4	KIN 3	KIN 9	KIN 10		Corporate ID	KIN 1	KIN 2	KIN 7	KIN 8	KIN 4	KIN 3	KIN 9	KIN 10	
CDD-000295	44.0	57.0	28.0	1.0	24.0	21.0	46.0	-3.0		CDD-000330	2.0	-13.0	-6.0	-6.0	12.0	53.0	5.0	17.0	
CDD-000296	-4.0	7.0	-8.0	12.0	3.0	12.0	-6.0	13.0		CDD-000331	-11.0	3.0	-7.0	-39.0	23.0	9.0	11.0	-2.0	
CDD-000297	61.0	68.0	-5.0	31.0	99.0	78.0	0.0	5.0		CDD-000332	-2.0	-1.0	-12.0	-37.0	15.0	17.0	10.0	16.0	
CDD-000298	27.0	17.0	-7.0	33.0	55.0	35.0	41.0	5.0		CDD-000333	-3.0	-6.0	-4.0	-90.0	6.0	15.0	13.0	-8.0	
CDD-000299	-1.0	-7.0	-14.0	-12.0	1.0	10.0	-4.0	15.0		CDD-000334	-3.0	-10.0	-10.0	-50.0	9.0	3.0	9.0	2.0	
CDD-000300	16.0	35.0	-7.0	-33.0	12.0	12.0	0.0	28.0		CDD-000335	-7.0	5.0	-6.0	17.0	24.0	24.0	1.0	2.0	
CDD-000301	21.0	7.0	1.0	-36.0	17.0	28.0	38.0	2.0		CDD-000336	-2.0	-27.0	-3.0	18.0	-24.0	15.0	1.0	7.0	
CDD-000302	12.0	10.0	1.0	-13.0	14.0	7.0	9.0	18.0		CDD-000337	0.0	3.0	4.0	21.0	18.0	15.0	-6.0	15.0	
CDD-000303	68.0	94.0	53.0	9.0	13.0	9.0	80.0	35.0		CDD-000338	13.0	-7.0	4.0	4.0	22.0	3.0	-5.0	7.0	
CDD-000304	6.0	1.0	9.0	34.0	17.0	19.0	34.0	16.0		CDD-000341	19.0	25.0	5.0	56.0	26.0	80.0	0.0	19.0	
CDD-000305	4.0	-6.0	-1.0	2.0	10.0	15.0	8.0	21.0		CDD-000342	5.0	-9.0	-7.0	-14.0	14.0	17.0	-1.0	14.0	
CDD-000306	82.0	28.0	67.0	94.0	26.0	-16.0	81.0	3.0		CDD-000343	22.0	21.0	19.0	-32.0	26.0	48.0	66.0	8.0	
CDD-000307	93.0	97.0	135	84.0	100	99.0	101	174		CDD-000344	13.0	3.0	6.0	5.0	26.0	19.0	21.0	43.0	
CDD-000308	5.0	17.0	-9.0	-21.0	31.0	-1.0	-1.0	10.0		CDD-000345	-20.0	7.0	-7.0	60.0	34.0	84.0	12.0	3.0	
CDD-000309	7.0	18.0	-10.0	-45.0	9.0	10.0	3.0	-4.0		CDD-000346	26.0	18.0	23.0	68.0	56.0	61.0	78.0	20.0	
CDD-000310	5.0	15.0	-8.0	45.0	49.0	9.0	66.0	14.0		CDD-000347	23.0	5.0	16.0	67.0	20.0	29.0	36.0	51.0	
CDD-000311	91.0	90.0	73.0	98.0	85.0	95.0	83.0	56.0		CDD-000348	63.2	36.5	35.6	45.0	37.0	25.9	70.7	99.0	
CDD-000312	74.0	94.0	80.0	81.0	24.0	5.0	43.0	3.0		CDD-000350	2.0	3.0	-2.0	-34.0	13.0	10.0	5.0	12.0	
CDD-000313	8.0	81.0	-8.0	46.0	4.0	22.0	-3.0	-3.0		CDD-000361	17.0	19.0	0.0	27.0	47.0	64.0	26.0	18.0	
CDD-000314	-83.0	-90.0	-428	-55.0	15.0	8.0	-23.0	-65.0		CDD-000362	21.0	27.0	-6.0	32.0	12.0	59.0	9.0	14.0	
CDD-000315	-37.0	28.0	-26.0	24.0	7.0	5.0	20.0	2.0		CDD-000363	7.0	13.0	0.0	57.0	17.0	28.0	20.0	36.0	
CDD-000316	23.0	16.0	-19.0	-28.0	77.0	43.0	5.0	10.0		CDD-000364	7.0	-1.0	5.0	33.0	4.0	12.0	7.0	19.0	
CDD-000317	8.0	-9.0	-22.0	-83.0	25.0	19.0	13.0	-7.0		CDD-000415	57.0	88.0	-11.0	21.0	39.0	21.0	2.0	5.0	
CDD-000318	3.0	14.0	-26.0	-39.0	10.0	10.0	8.0	1.0		CDD-000416	-27.0	13.0	9.0	28.0	35.0	1.0	3.0	5.0	
CDD-000319	5.0	-7.0	-11.0	8.0	15.0	3.0	-5.0	23.0		CDD-000417	-3.0	15.0	14.0	36.0	15.0	5.0	-2.0	2.0	
CDD-000320	2.0	12.0	-12.0	13.0	5.0	15.0	-5.0	19.0		CDD-000432	54.0	10.0	34.0	49.0	14.0	3.0	30.0	15.0	
CDD-000321	1.0	-9.0	0.0	28.0	15.0	4.0	-1.0	9.0		CDD-000433	52.0	-17.0	6.0	74.0	16.0	4.0	53.0	-43.0	
CDD-000322	-1.0	-4.0	-295	-4.0	14.0	10.0	11.0	18.0		CDD-000434	81.0	20.0	65.0	30.0	35.0	17.0	64.0	50.0	
CDD-000323	4.0	-6.0	-4.0	-16.0	8.0	4.0	-4.0	34.0		CDD-000435	73.0	15.0	53.0	-9.0	22.0	14.0	25.0	43.0	
CDD-000324	10.0	-8.0	-3.0	29.0	68.0	19.0	0.0	30.0		CDD-000436	92.0	-3.0	81.0	70.0	-1.0	8.0	86.0	-52.0	
CDD-000325	11.0	-2.0	-3.0	-59.0	12.0	27.0	1.0	31.0		CDD-000437	69.0	53.0	69.0	68.0	32.0	-25.0	83.0	32.0	
CDD-000326	16.0	16.0	-6.0	-31.0	16.0	12.0	-9.0	24.0		CDD-000438	24.0	6.0	50.0	51.0	-3.0	10.0	1.0	7.0	
CDD-000327	-2.0	-6.0	-7.0	7.0	2.0	23.0	4.0	0.0		CDD-000439	81.0	67.0	90.0	30.0	0.0	2.0	2.0	18.0	
CDD-000328	-7.0	-6.0	-1.0	14.0	14.0	10.0	-1.0	0.0		CDD-000440	96.0	96.0	102	69.0	8.0	9.0	42.0	20.0	
CDD-000329	0.0	-8.0	-14.0	18.0	10.0	16.0	0.0	14.0											

\*Circled compounds indicate starting points for specific kinases

< 40% Inhibition
40% - 80% Inhibition
> 80% Inhibition

# Competitive Landscape

## *KINect™ has Comprehensive Cysteinome Coverage*

Technology Capabilities	Irreversible Kinase Technology Companies		
	KINect™ Platform	Celgene Avilomics Research	Principia Biopharma
Target Specific	Yes	Yes	Yes
Broad cysteinome coverage	<b>Yes</b>	<b>No</b>	<b>No</b>
Multiple scaffolds/templates	<b>8-10</b>	<b>Patents limited to 1-2</b>	<b>Patent limited to 1</b>
Structure-based design enabled	Yes	Yes	Yes
Biochemical characterization ensuring specificity	Yes	Yes	Yes

The Cysteinome-directed KINect™ Platform is unique as it provides comprehensive coverage of the cysteinome potentially allowing for rapid and efficient drug discovery



# KINect™ Technology Platform: Summary

- The Aclaris fully integrated kinase drug discovery team has successfully utilized multiple novel approaches to generate drug candidates for disease relevant kinases
- The success of the MK2, ITK and JAK programs is linked to successful utility of the KINect™ platform
- The KINect™ compound library has been validated as a systematic approach to rapidly generate lead matter for hard to drug targets across the cysteinome
- We have successfully exploited the platform to generate composition of matter IP on lead series in less than half the typical time compared with conventional screening approaches
- We have identified chemistry hits and lead optimization starting points for 10 biologically interesting kinase targets for portfolio reload using KINect™
- Several of the top pharma companies and numerous biotech organizations contract drug research efforts with Confluence/Aclaris
- We have been instrumental in advancing partner company programs including the successful design and generation of drug lead compounds



EMPOWERING PATIENTS THROUGH  
**REVELATIONARY**  
SCIENCE

**ATI-450: MK2 Inhibitor**  
(an investigational compound)

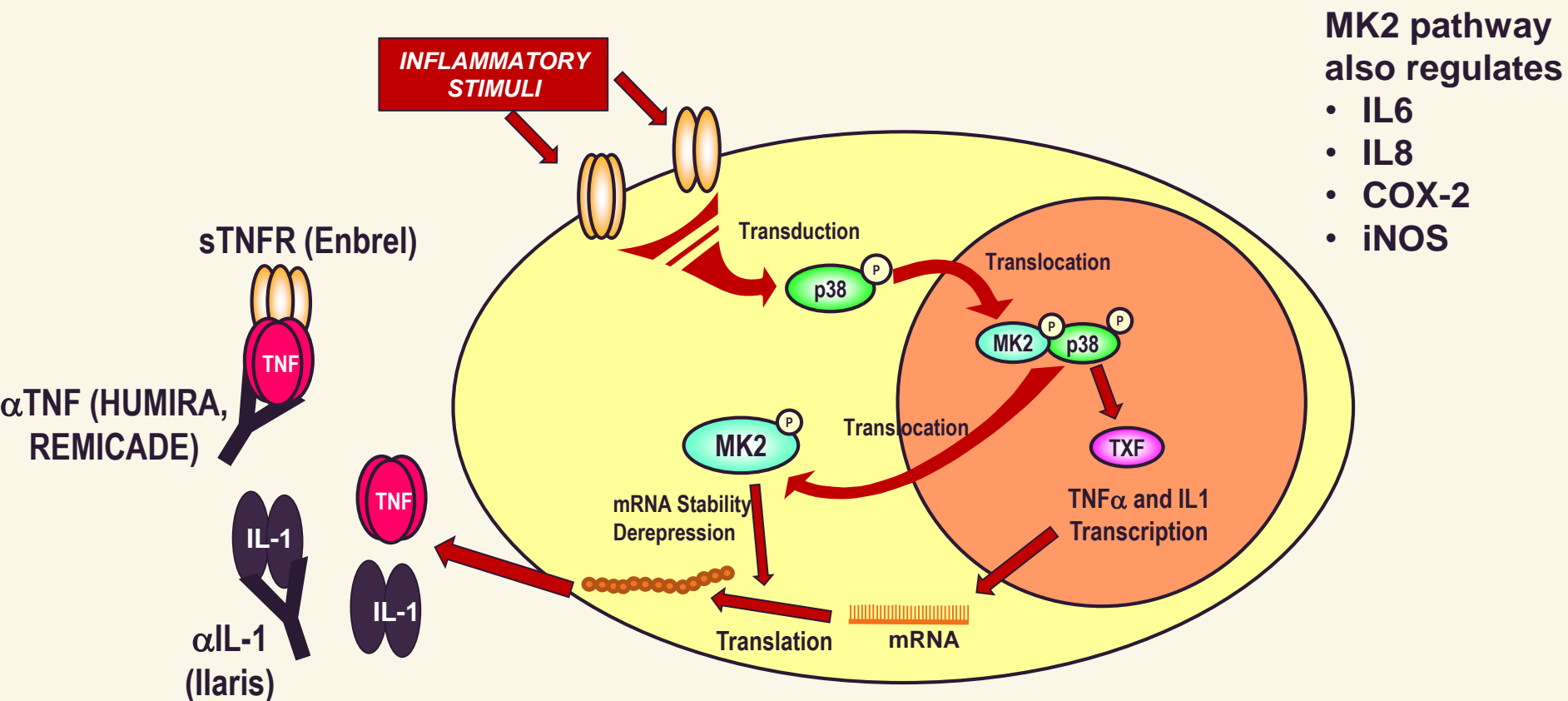


# MK2 Inhibitor – Potential ORAL Alternative to Injectable, Anti-Cytokine Biologics and JAK Inhibitors for Immuno-Inflammatory Diseases

- MK2\* is an attractive drug target because it drives pro-inflammatory cytokine expression associated with the p38 MAP kinase pathway
- The effects of inhibiting MK2 mirror the effects of anti-inflammatory biologics<sup>1</sup>
  - **anti-TNF:** HUMIRA<sup>®</sup>, ENBREL<sup>®</sup>, REMICADE<sup>®</sup>
  - **anti-IL1:** KINERET<sup>®</sup>, ILARIS<sup>®</sup>, ARCALYST<sup>®</sup>
  - **anti-IL6:** KEVZARA<sup>®</sup>, ACTEMRA<sup>®</sup>
- ATI-450 successfully inhibits MK2 via a novel MOA which involves the creation of and binding to a targetable drug "pocket"
- ATI-450 currently in Ph 1 clinical trial with data expected by YE19

# Intracellular Pathways Regulate Cytokine Production

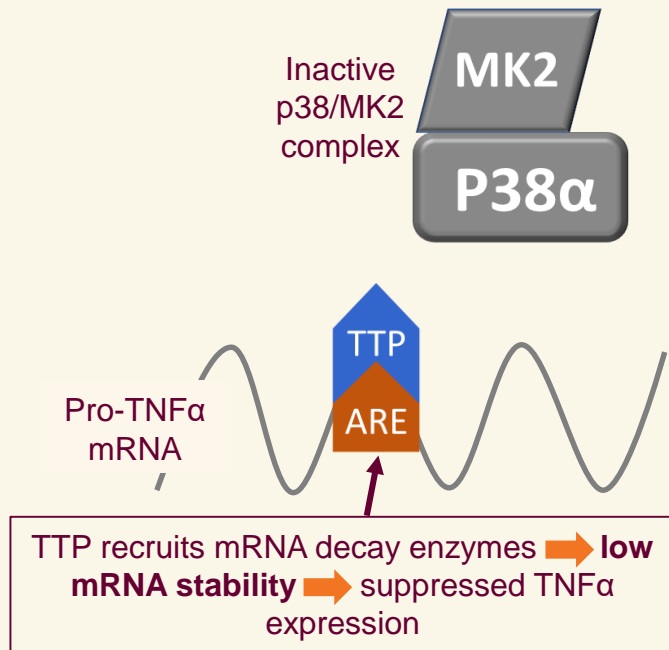
## *MK2 pathway required for IL-1 and TNF $\alpha$ biosynthesis*



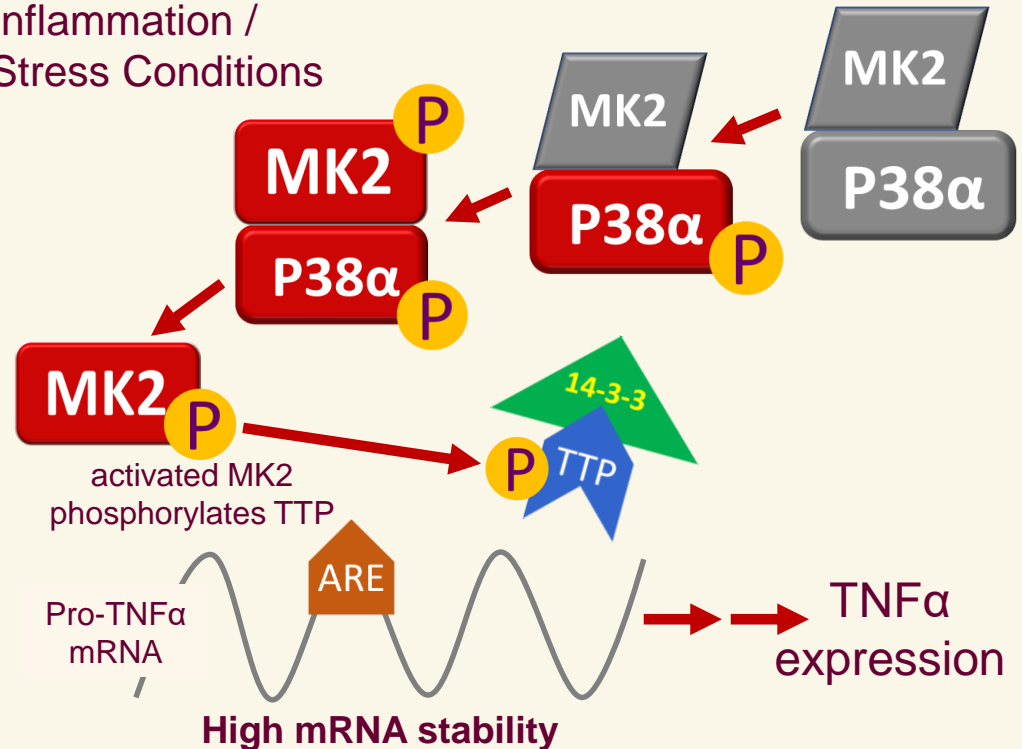
# MK2 Post-Transcriptionally Regulates TNF $\alpha$ and Other Key Pro-Inflammatory Cytokines

## MK2 Regulates Post-Transcriptional mRNA Stability

### Resting Conditions



### Inflammation / Stress Conditions



- Tristetraprolin (TTP) is a post-transcriptional regulator that controls mRNA stability
- AREs = AU-rich mRNA elements that act as binding platforms for TTP
- 14-3-3 proteins sequester phosphorylated TTP, preventing its mRNA degrading activity

Activated MK2, released from the p38/MK2 complex, phosphorylates substrates within both the nucleus and the cytoplasm. Within the nucleus, one of MK2's activities is to phosphorylate TTP



Inactive kinase



Active kinase



Phosphate group

# Historical Development of p38 Inhibitors:

## *Off-target tox, on-target tox, tachyphylaxis*

- 1<sup>st</sup> generation failed due to safety profile
  - Off-target effects – poor kinase selectivity
  - On-target tox liabilities
- 2<sup>nd</sup> generation were very selective with fewer off-target toxicities
  - On-target tox liabilities remain
  - In the clinic – tachyphylaxis in rheumatoid arthritis (RA) & inflammatory bowel disease (IBD)
  - Tachyphylaxis may reflect p38 inhibitors down-regulating anti-inflammatory pathway

MK2 inhibitors, *in contrast to p38 inhibitors*, appear to:

- Have excellent kinase selectivity
- Do not affect other p38 substrate pathways
- Spare p38 anti-inflammatory pathways (diminished tachyphylaxis risk)

Team collectively has over 100 years experience in the pathway

1 Charron et al. 2017. RV568, a narrow spectrum kinase inhibitor with p38 MAPK- $\alpha$  and - $\gamma$  selectivity suppresses COPD inflammation. Eur Respir J

2 Coulthard et al, 2009. p38 MAPK: stress responses from molecular mechanisms to therapeutics. Trend Molec Med

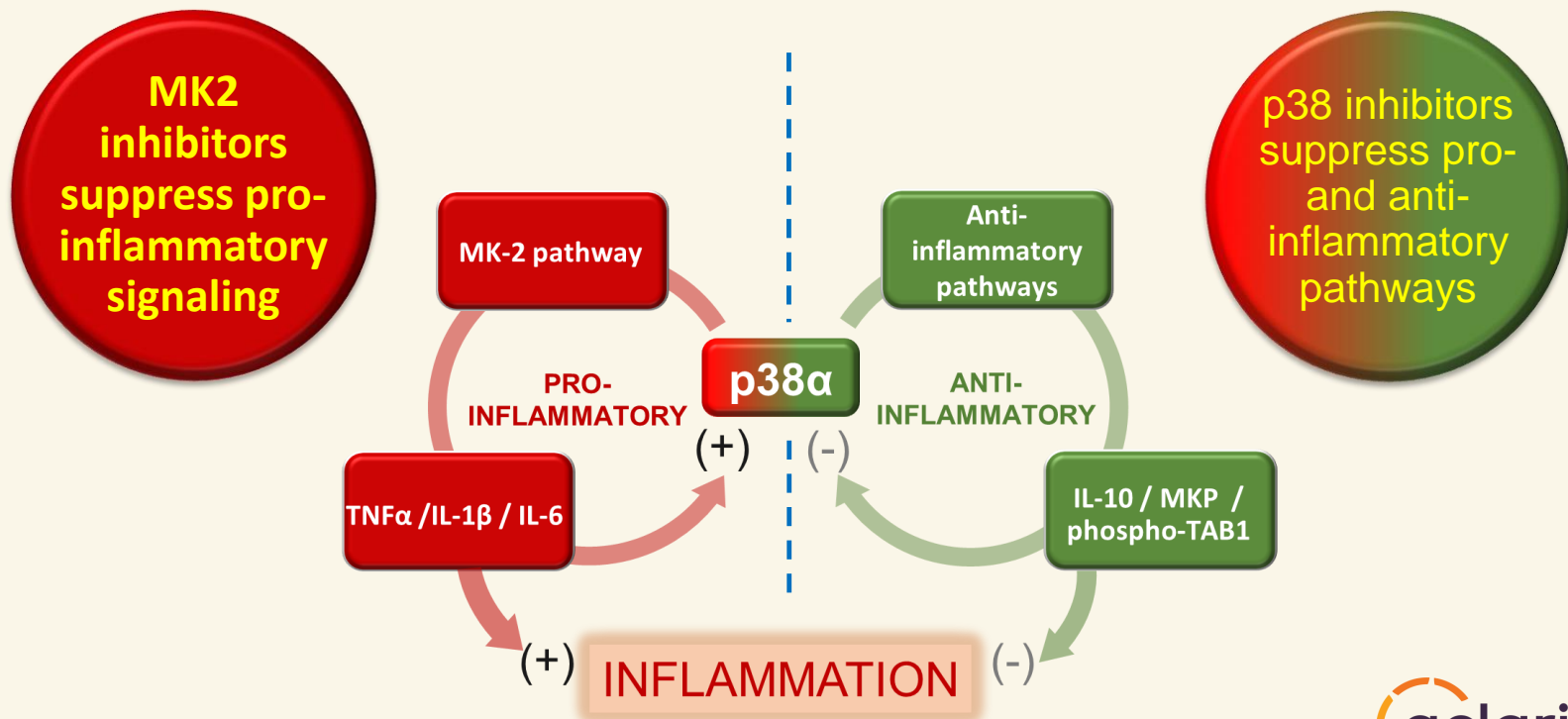
3 Schindler et al. 2007. p38 pathway inhibitors as anti-inflammatory drug targets. J Dent Res

# p38 MAPK Substrates

Transcription Factor	DNA Binding	Regulatory Protein	RNA Binding
Atf2	BAF60c	BimEL-BCL2L11	FBP2/3
C/EBP $\beta$	CDt1	Caspase-3-CASP3	HuR-ELAV1
CHOP-GADD153-DDIT3	E47-TCF3	Caspase-8-CASP8	KSRP
ERa-ESR1	SRC3-NCOA3	Cdc25A	SP45-RBM17
Fos-c-fos	H3-H3F3A	Cdc25B	Membrane
FOXO3a	HBP1	Cyclin D1-CCND1	EGFR
Jun-c-Jun	p18Hamlet-ZNHIT1	Cyclin D3-CCND3	FGFR1
MAfA	PGC-1a	FLIPs-CFLAR	Nav1.6-SCN8A
MEF2A	Rb1	GS-GYS1	NHE1
MEF2C	Ser/Thr Kinase	JIP4-SPAG9	TACE-ADAM17
MITF	GSK3 $\beta$	p47phox-NCF1	Endosome
MRF4-MYF6	MK2-MAPKAPK2	p57kip2-CDKN1C	EEA1
p53-TP53	MK3-MAPKAPK3	PIP4K $\beta$ -PIP4K2B	GDI-2
Smad3	MK5-PRAK-MAPKAPK5	Rpn2-PSMD1	Rabenosyn5-ZFYVE20
STAT1	Mnk1-MKNK1	Siah2	Structural
STAT4	Mnk2-MKNK2	Tab1	Hsp27-HSPB1
Usf1	Msk1-RPS6KA4		Keratin 8
Xbp1s	PKC $\epsilon$		Lamin B1

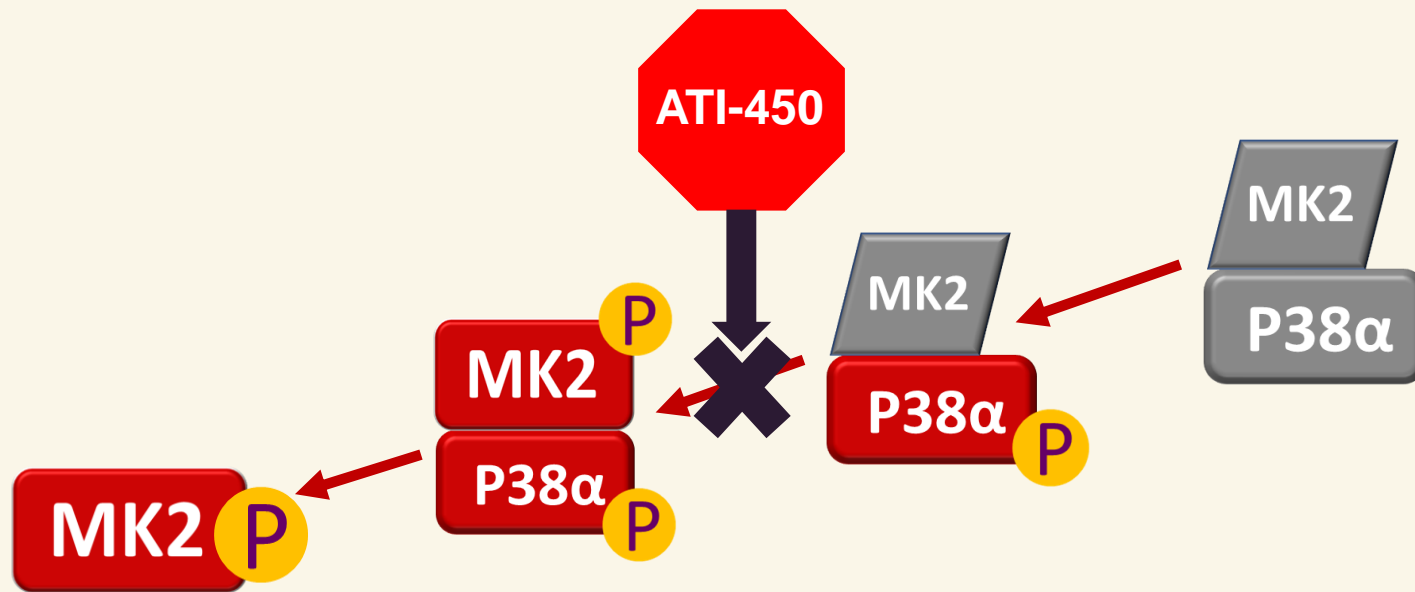
# The Path From p38 to MK2

- p38 was the original therapeutic target for suppressing TNF $\alpha$  and other pro-inflammatory cytokines
- Historically p38 inhibitors could not overcome toxicity and demonstrated a lack of sustained activity in certain diseases such as RA and IBD. This lack of sustained activity, or tachyphylaxis, may have resulted from conflicting anti- and pro-inflammatory effects.



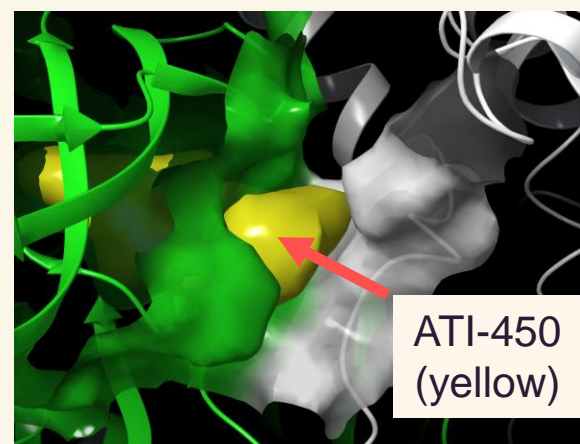
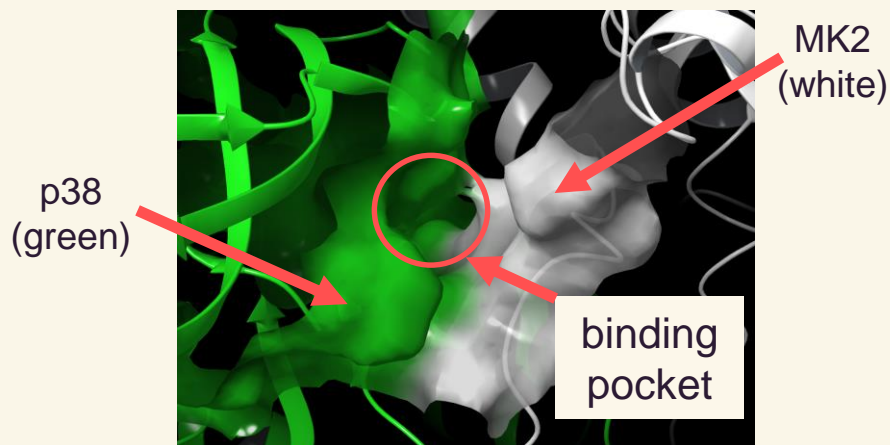


# ATI-450 Blocks MK2 Activation, BUT NOT p38 Phosphorylation of Other Substrates



- ATI-450 “captures” MK2 in an inactive state – preventing p38MAPK from phosphorylating/activating MK2
- ATI-450 is substrate selective. It is designed to only interact with the p38-MK2 complex and not other p38 substrates

# Capturing MK2 in an Inactive State



Crystal structure of the p38α/MK2 complex

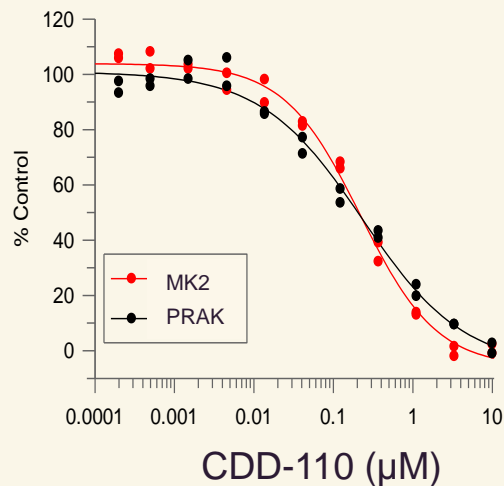
ATI-450 (yellow) docked in the pocket

- In the nucleus, inactive MK2 and p38 dock in a high affinity complex that exhibits a binding pocket formed by juxtaposed walls of both proteins
- Aclaris MK2 inhibitors bind to both walls of the pocket, stabilizing the complex and preventing MK2 activation

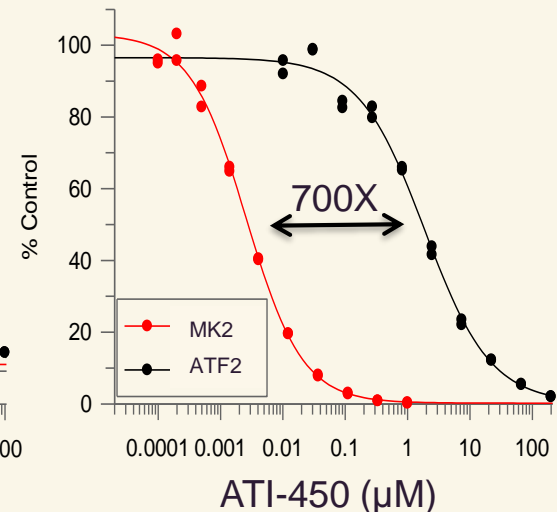
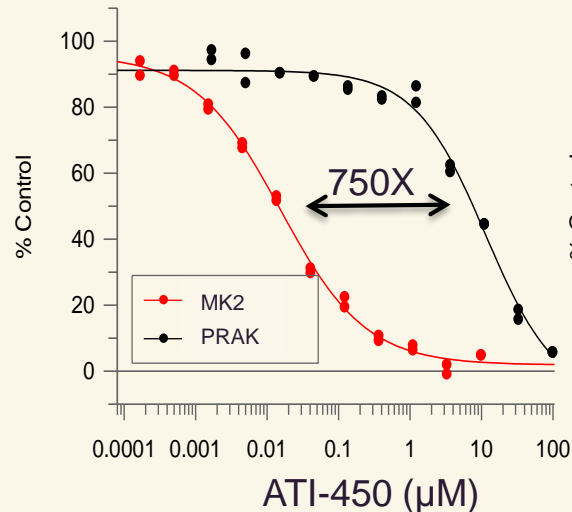
Aclaris MK2 inhibitors lock MK2 in a catalytically inactive state – a unique MOA

# ATI-450 is Highly Selective for MK2 vs other p38 Substrates

CDD-110, a global p38 inhibitor, inhibits MK2 and PRAK (MK5) with equal potency



ATI-450 inhibits MK2  $\geq 700\text{X}$  more potently than it does either PRAK or ATF2 (a p38 activated transcription factor)

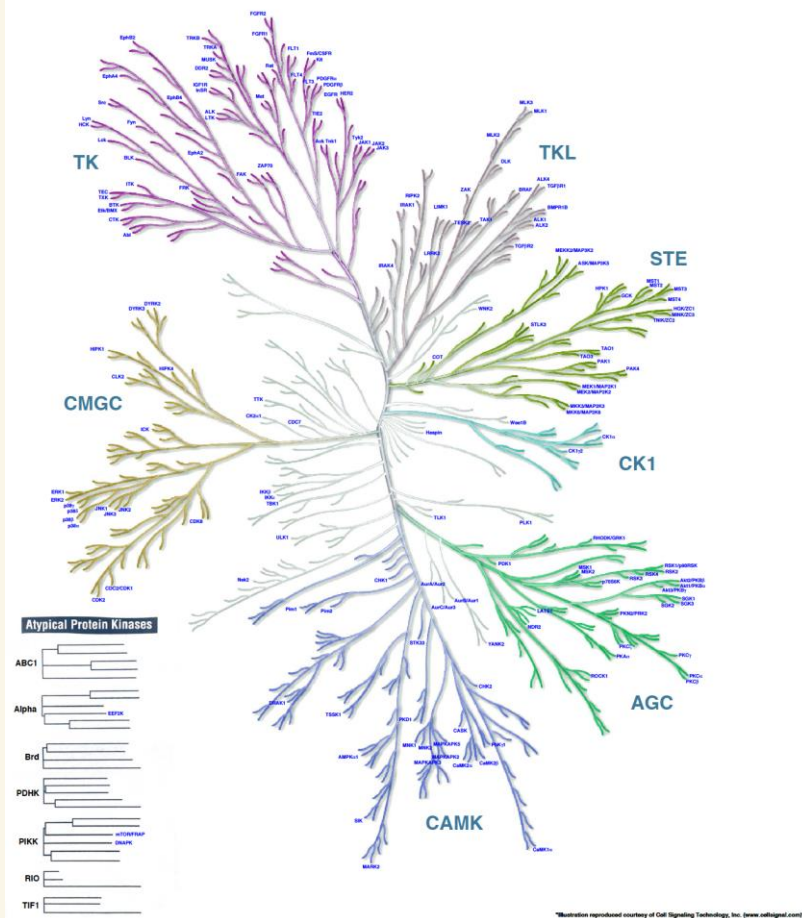


ATI-450 is highly selective inhibitor of MK2, essentially sparing the activity of all other p38 substrates

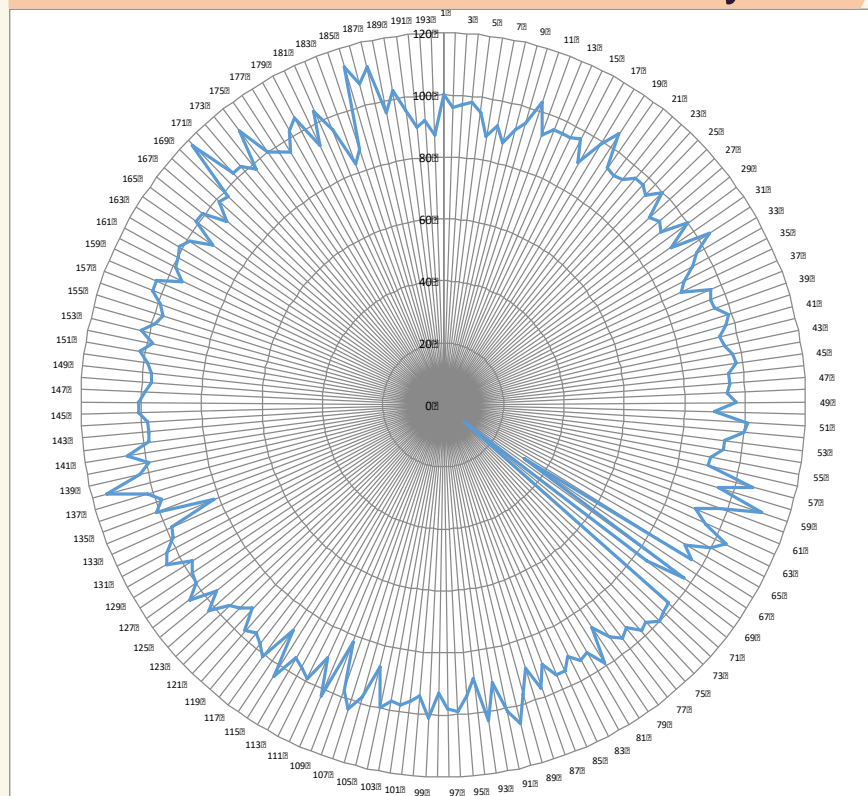
- Reduced toxicity risks
- Reduced risk for tachyphylaxis

# ATI-450 Selectivity

## Kinase Panel



## Human Kinome Selectivity



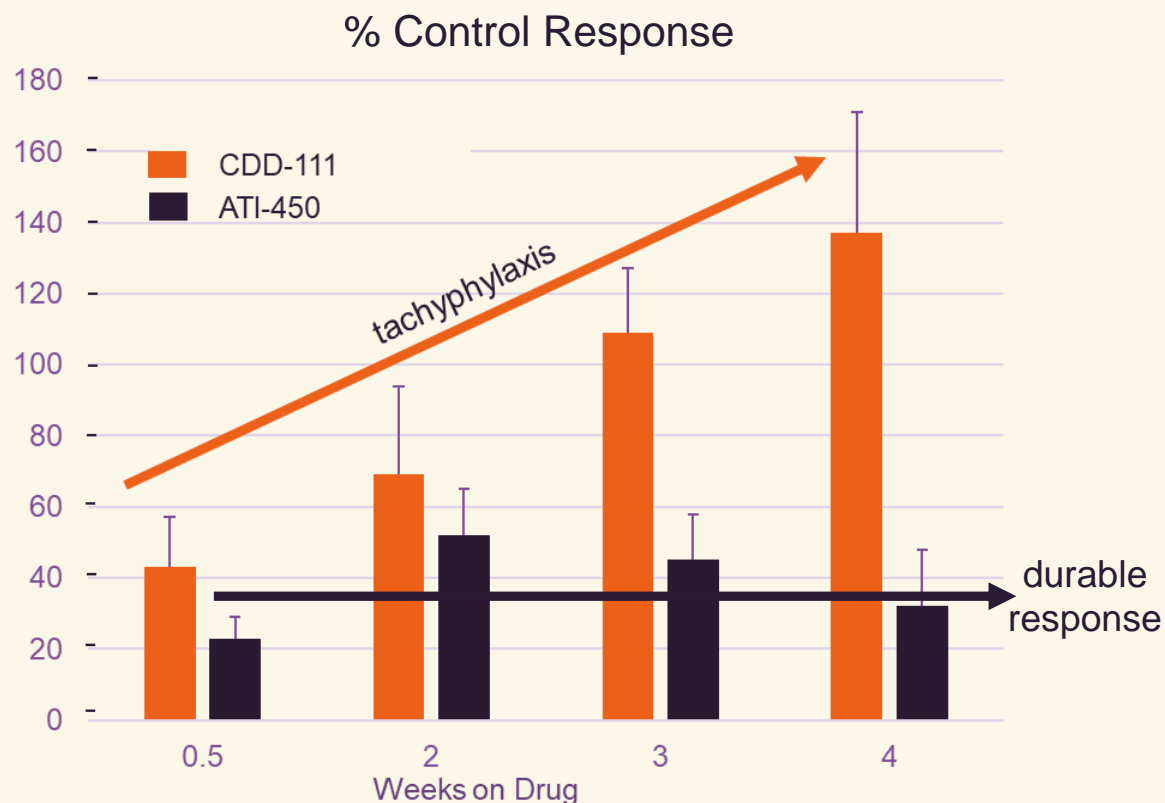
- >350-fold binding selectivity on all kinases in this panel except p38 $\alpha$  and p38 $\beta$
- In total, ATI-450 tested vs 193 kinases at 5  $\mu$ M and found selective

# ATI-450: MK2 inhibitor - Anti-inflammatory Data

(an investigational compound)

# Mouse Model: ATI-450 Durable Response *in vivo*

## LPS-induced TNF $\alpha$ Expression in Mice



### Protocol:

- p38 inhibitor (CDD-111) or ATI-450 administered to mice in feed starting day 1 and continuing through day 28
- LPS challenges and blood TNF $\alpha$  levels determined at Days 4, 14, 21 and 28
- Drug levels in blood were quantified to control for changes in drug metabolism

- p38 inhibitor lost efficacy as a function of time (tachyphylaxis)
- ATI-450 exhibits durable efficacy during 4-week study

# Animal Models Supporting the Development of MK2 inhibitors in Inflammatory Diseases

Therapeutic area	Model (all used ATI-450)	Reference
Rheumatoid Arthritis / Osteoarthritis / Psoriatic Arthritis	Rat streptococcal cell wall arthritis model <ul style="list-style-type: none"><li>- Protection against bone deterioration</li><li>- Protection against lethality</li></ul> Inhibition of cellular IL1 $\beta$ mRNA stability & translation	Wang, et al., 2018, J Ex Med 215:1315
Inflammatory Bowel Disease / Crohn's	Adoptive transfer model of colitis <ul style="list-style-type: none"><li>- Endoscopy scores show disease control</li><li>- Decreased inflammatory infiltrate</li><li>- Protected structural integrity of mucosa</li></ul>	Haigis, et al., 2019 Integrative Biology, In press
Cryopyrin-Associated Periodic Syndromes (CAPS)	Murine NOMID (severe form of CAPS) transgenic model Human CAPS PBMC* IL1 $\beta$ modulation	Wang, et al., 2018 J Ex Med 215:1315

\* PBMC = Peripheral blood mononuclear cells

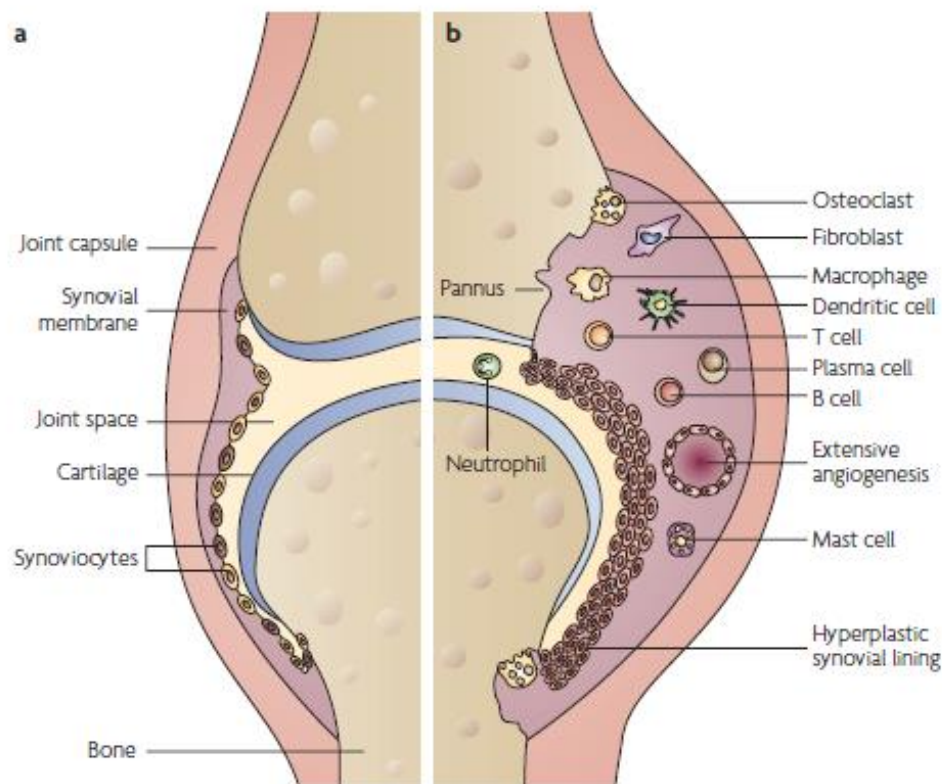


# ATI-450 by blocking MK2 – Potential Effect in Rheumatoid Arthritis

MK2 is a key regulator of essential pathogenic signals in chronic inflammatory and autoimmune diseases

Normal

RA



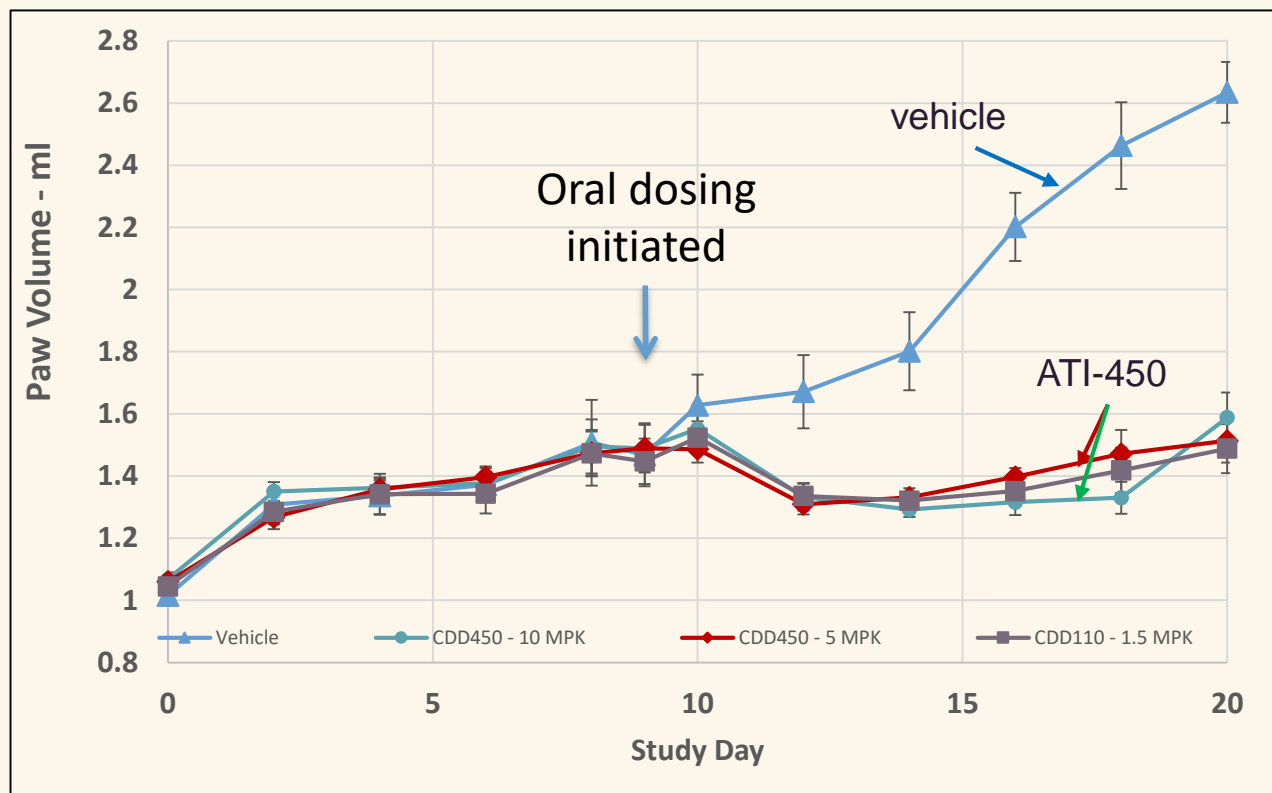
Cells	Cytokines	Mediators
Monocyte/Macrophage	<b>TNF<math>\alpha</math></b>	COX-2
Osteoclast	<b>IL1<math>\beta</math></b>	iNOS
Epithelial Cells	<b>IL1<math>\alpha</math></b>	MMP-9
Synovial Fibroblast	<b>IL6</b>	
Chondrocytes	<b>IL18</b>	
	<b>RANKL</b>	

\*Bolded Above is ATI-450 data on file

# Rat Model: ATI-450 Activity in Rat Streptococcal Cell Wall Arthritis

## Protocol

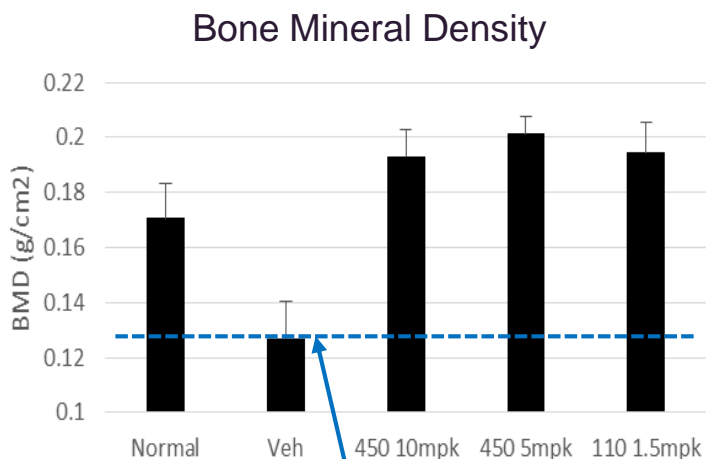
- On Day 0, rats were injected IP with SCW prep.
- The acute phase of the disease induces paw edema between Day 2 and Day 8.
- On Day 9, compound dosing initiated.
- The edema is monitored every other day until Day 21.
- On Day 21, the study was terminated, trough blood levels obtained, and paws collected for bone density determination.
- CDD110 is a conventional global p38 inhibitor.



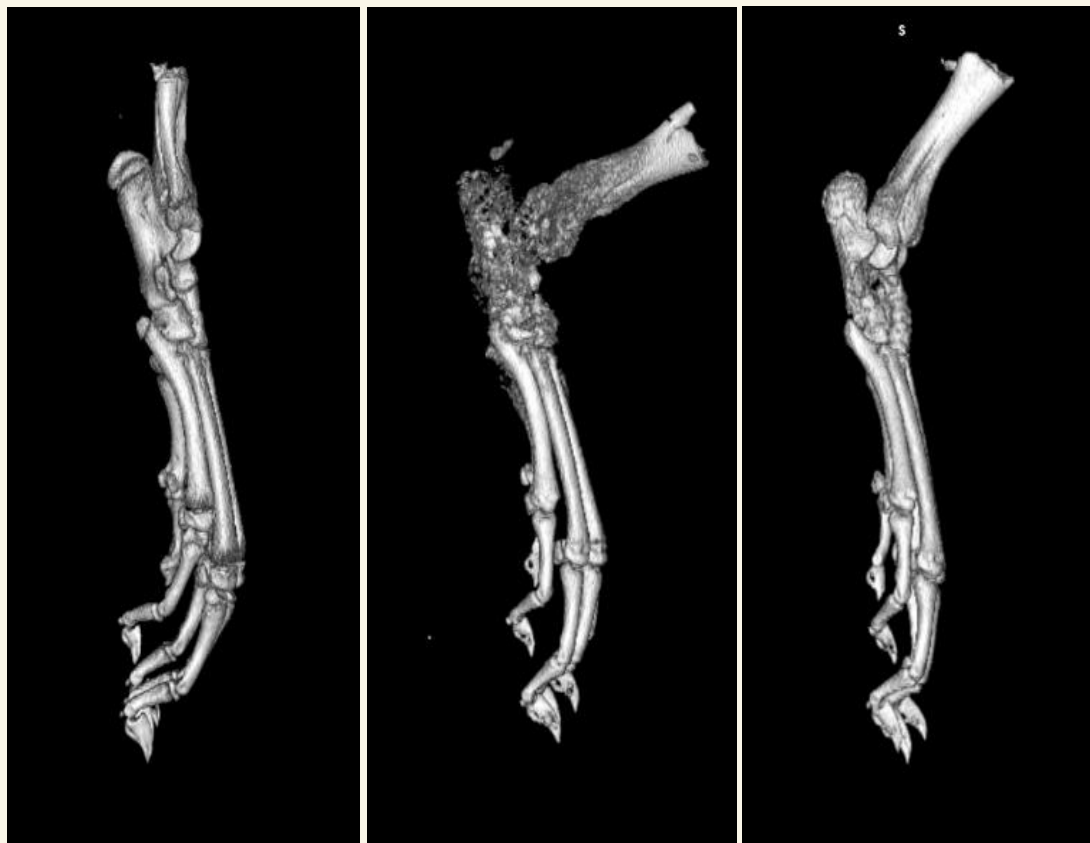
ATI-450 activity is comparable to “Rat-Enbrel” (historical data)

# Rat Model: ATI-450 Activity in Rat Streptococcal Wall Arthritis Model: Disease Modifying Activity – Joint and Bone Preservation

- Significant deterioration of the ankle joint observed in disease (middle panel)
- Bone protection with ATI-450 (right panel)
- Bone mineral density confirms protection (below)



Loss of bone mineral density in control cohort



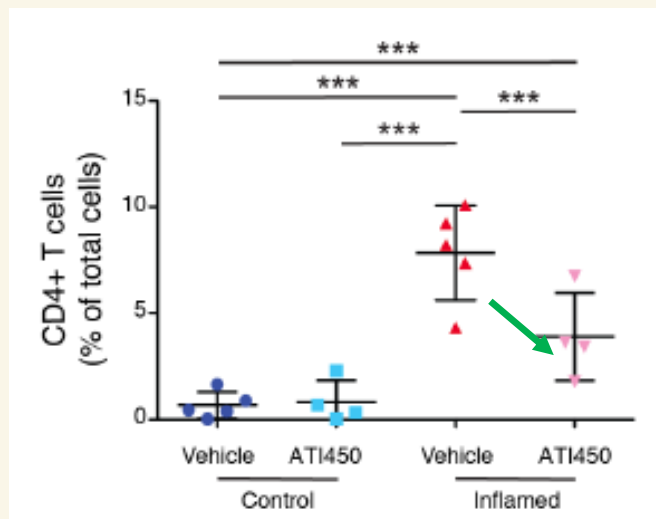
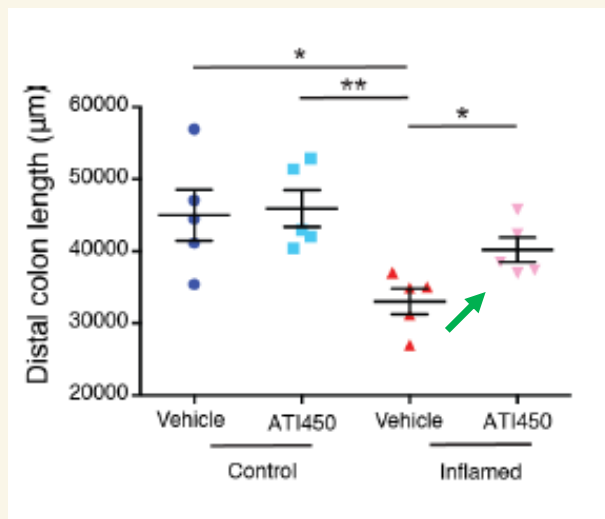
Control

Vehicle

ATI-450 (5mpk)

# Mouse Model: Orally Dosed ATI-450 in an Adoptive Transfer Mouse Model of Crohn's Colitis

- Collaboration with Dr. Kevin Haigis, Harvard Medical School
- Adoptive transfer of CD4+CD45RB<sup>hi</sup> T cells (naïve T cells) into RAG-1<sup>-/-</sup> mouse (no endogenous T or B cells); Synchronously develop intestinal colitis 6-8 weeks post transfer
- At time of disease development (as assessed by weight loss and confirmatory endoscopy) – ATI-450 Rx in chow begins
- After 14 days of treatment, colons analyzed for length, proliferation and T cell infiltrate

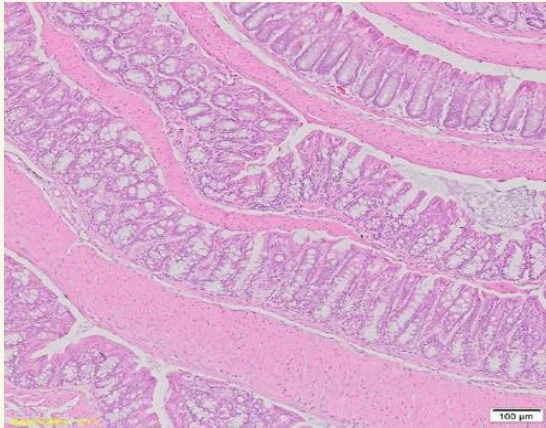


Endoscopy score / colon length data show improved disease as measured by

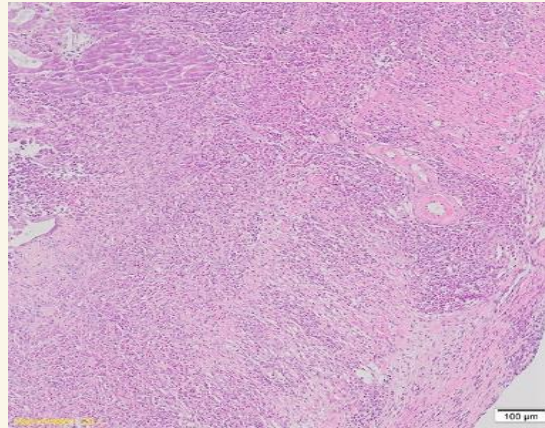
- colon length (longer is better), and
- reduced inflammation score (CD4+ T cells - lower is better)

# Mouse Model: Orally Dosed ATI-450 in a Crohn's Colitis Adoptive Transfer Model

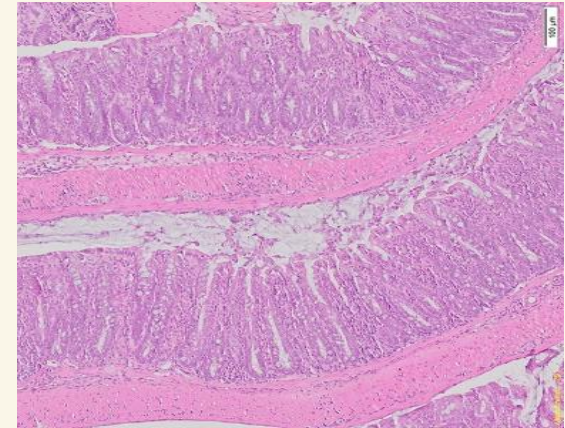
## Histopathology



Normal



Control  
(disease is expressed)



ATI-450  
(disease is suppressed)

## Histology shows

- decreased lymphoid infiltrate
- preserved crypt architecture

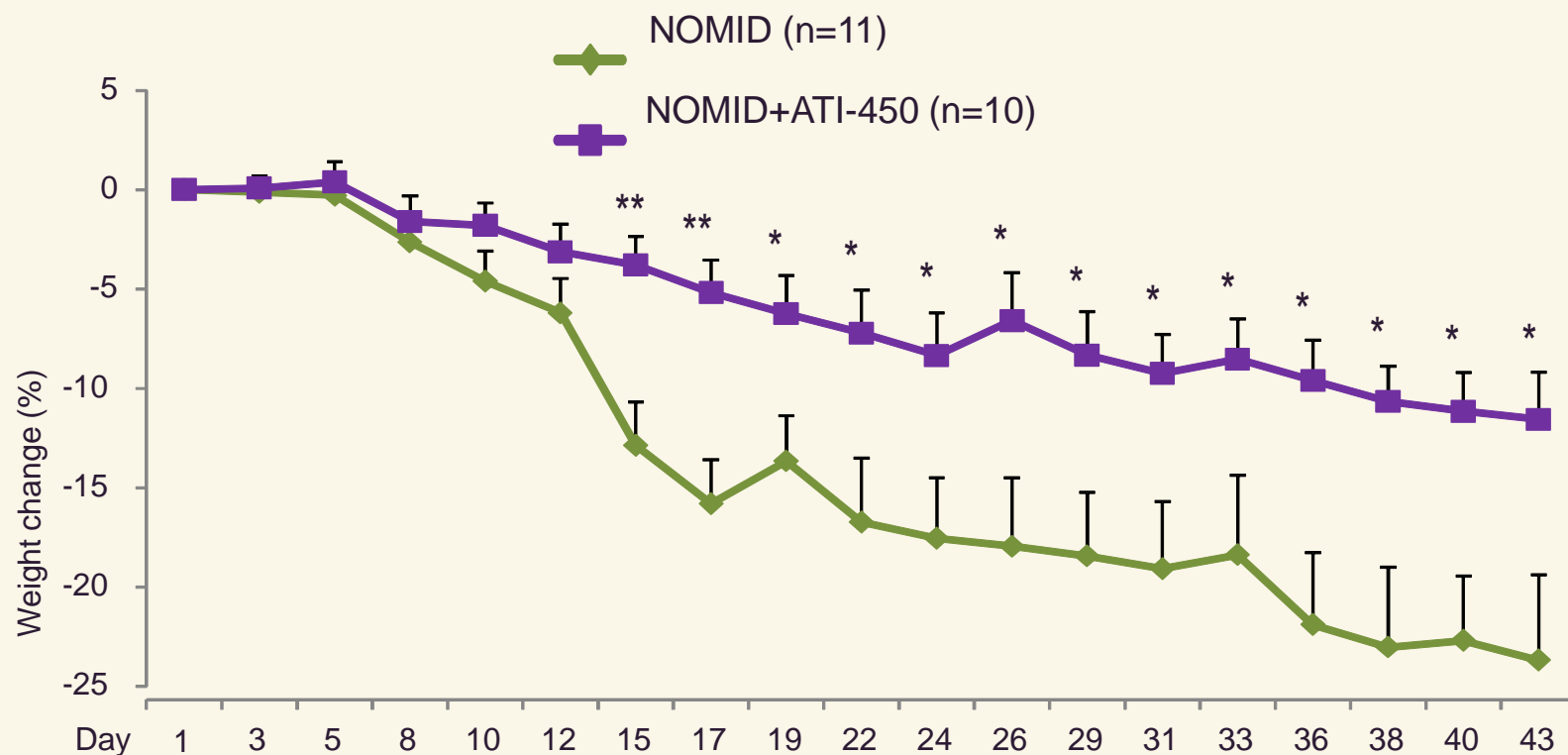
Orally administered ATI-450 suppresses the manifestations of adoptive T-cell colitis mouse model



# Mouse Model: ATI-450 Activity in a NOMID Model of CAPS

- Cryopyrin-Associated Periodic Syndromes (CAPS) are orphan, genetic disorders caused by NLRP3 inflammasome-activating mutations
  - IL1 $\beta$ -dominant pro-inflammatory cytokine profile
  - Symptoms:
    - Systemic inflammation, fevers, CNS symptoms, hearing/vision loss, retarded growth, skeletal deformities, joint pain, early death
    - Neonatal-onset multisystem inflammatory disease (NOMID) is the most severe phenotype
- Standard of care is anti-IL1 biologics (anakinra, canakinumab, rilonacept)
  - Efficacious against inflammatory symptoms, but less so against osteo/skeletal symptoms
  - Resistance develops against current biologics
- ATI-450 evaluated in a CAPS (NLRP3 / IL1 $\beta$ -dominant) model\*
  - NOMID mice express activated NLRP3
  - Protocol
    - 2-month-old male and female NOMID and WT mice
    - Feed with normal chow or ATI-450 chow, starting 3 d before tamoxifen
    - Inject 75 mg/kg tamoxifen, i.p., 3X every other day/week, 2 weeks
    - Measure body weight 3X/week
    - At sacrifice, analyze bones, macrophages, serum, bone marrow fluid

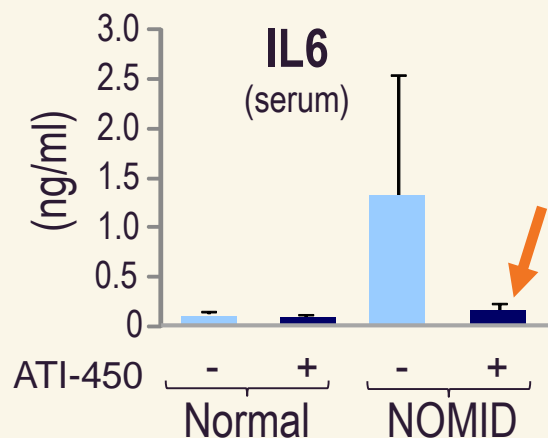
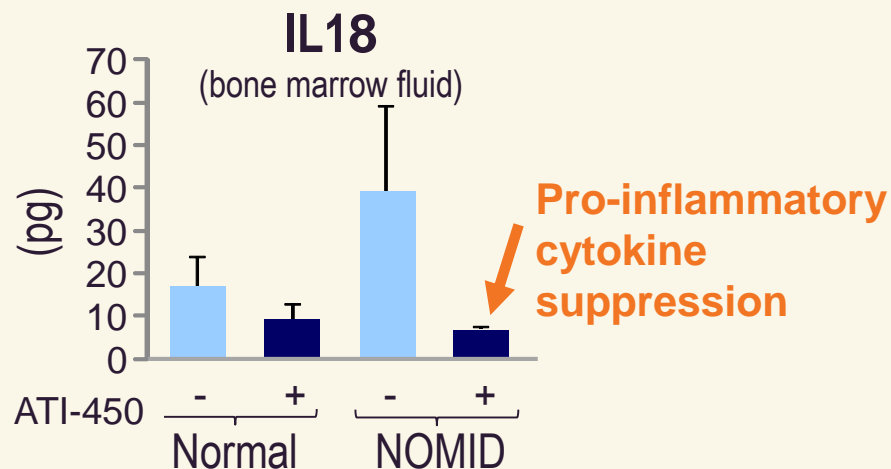
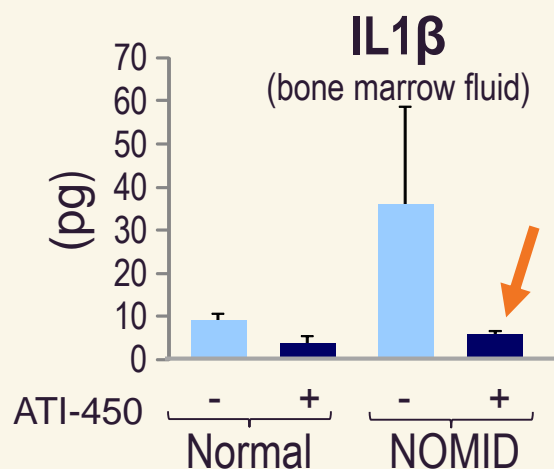
# Mouse Model: ATI-450 Protects Against Weight Loss in NOMID Mice



- Attenuated body weight loss
- Prevented death (no death in treated mice)
- Prevented development of splenomegaly
- Inhibited osteoclast formation
- Inhibited bone loss



# Mouse Model: ATI-450 Suppresses Inflammation in NOMID Mice



ATI-450  
PLACEBO

Orally dosed ATI-450 in NOMID mice suppresses the expression of IL1 $\beta$ , IL18, IL6

# Mouse Model: ATI-450 Inhibits RANKL-induced Osteoclastogenesis

Bone marrow derived macrophages (BMDM) from NOMID mice

- In CAPS, osteoclastogenesis gives rise to low bone mass (osteopenia)
- (a) When bone marrow derived macrophages (BMDM) from NOMID mice are stimulated with RANKL (RANK ligand), they differentiate into osteoclasts
- (b) ATI-450 blocks this macrophage differentiation

Macrophages

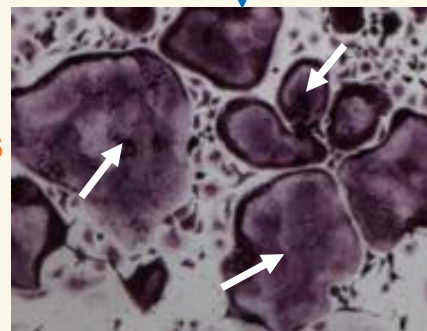
RANKL stimulation

Osteoclasts

NOMID BMDM



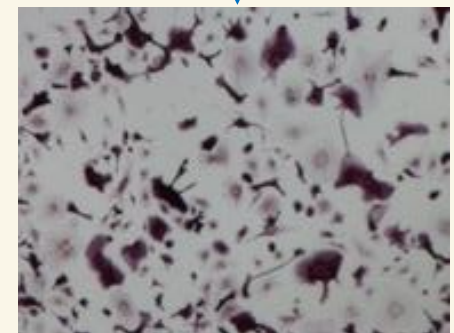
(a)



NOMID BMDM  
Plus ATI-450

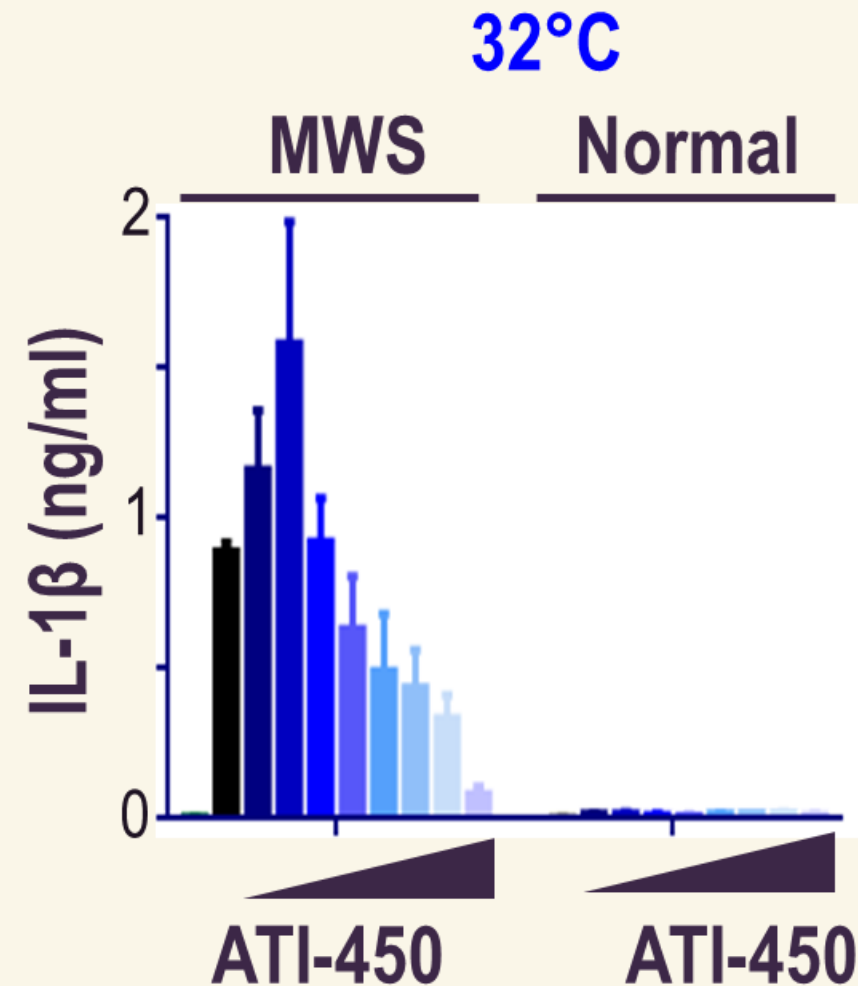


(b)



ATI-450 inhibits RANKL-stimulated macrophage differentiation into osteoclasts from NOMID mice

## Ex Vivo Data: ATI-450 Inhibits IL1 $\beta$ Expression in PBMCs from a CAPS Patient



- To evaluate how findings in mice might translate into humans, peripheral blood mononuclear cells were isolated from CAPS patients and healthy controls. In CAPS patients (Muckle Wells Syndrome; MWS), disease (reflected by IL1 $\beta$  expression) is triggered by exposure to low temperatures.
- CAPS PBMCs spontaneously produced high amounts of IL1 $\beta$  at 32°C but not at 37°C.
- ATI-450 blocks stress induced IL1 beta production.

# ATI-450: MK2 inhibitor - Development Status and IND-Related Studies (an investigational compound)

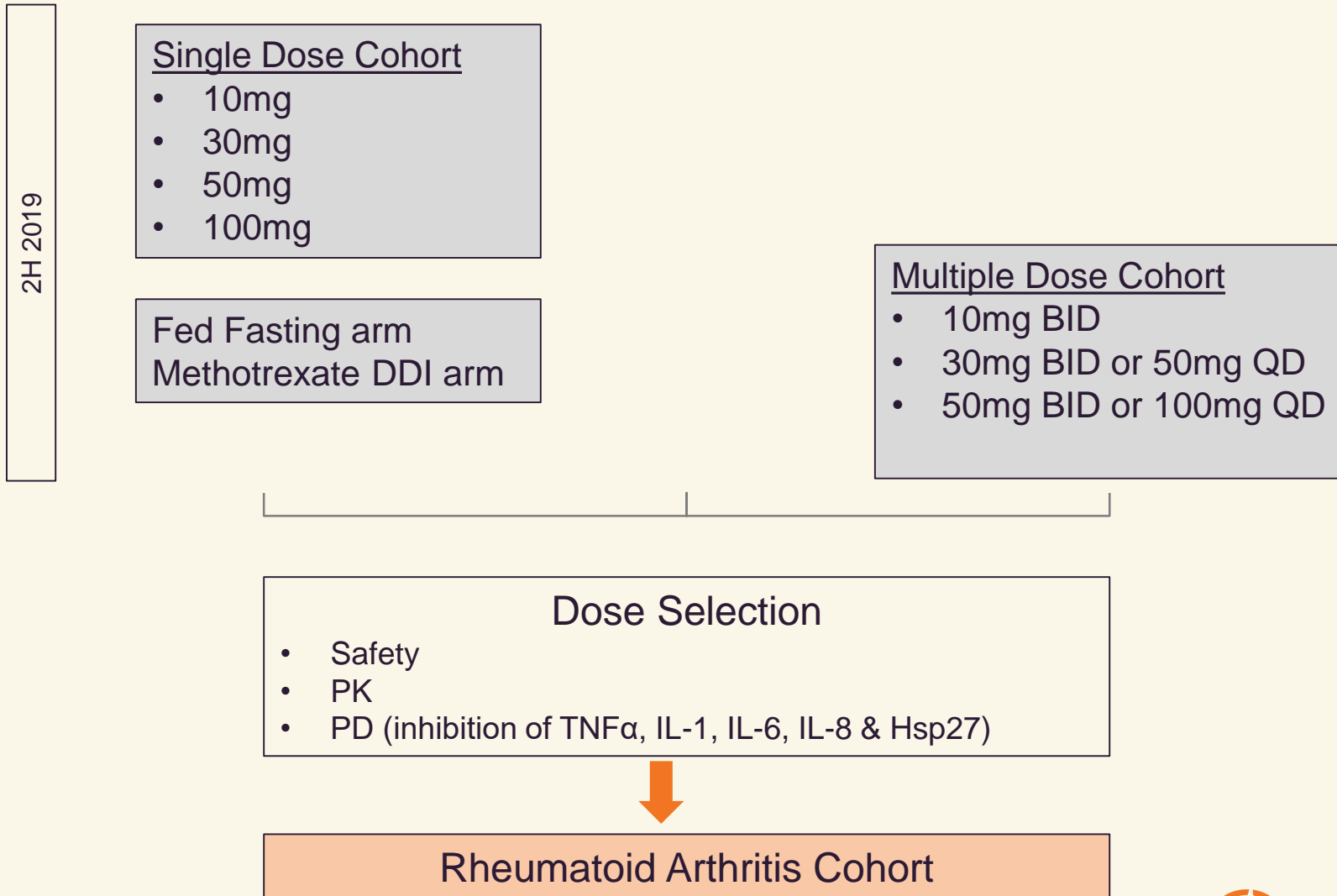
## ATI-450 IND Status

- IND open and currently in Ph 1 single and multiple ascending doses
- GLP toxicology
  - ✓ 28-day rat – no-observed-adverse-effect-level (NOAEL)
  - ✓ 28-day minipig
  - ✓ 13-week studies in rat and minipig (in-life completed)
- Safety pharmacology – all studies complete; no issues
  - ✓ CNS assessment (Irwin Test)
  - ✓ Respiratory assessment in rat
  - ✓ CV: *In vitro* hERG; radio-telemetry in mini-pig
  - ✓ Gene toxicology: Bacterial reverse mutation assay (AMES); *In vitro* chromosomal aberration; *In vivo* micronucleus
  - ✓ Broad ligand screen

# ATI-450 Pharmaceutical Development

- IP
  - ✓ Covered in USP 9,115,089
  - ✓ Four additional patent families around other MK2 pathway inhibitors filed
- Drug Substance
  - ✓ GMP synthesis: >6kg available
  - ✓ Ph IIB/III launch ready API manufacturing route and specification being optimized
- Formulation
  - ✓ Tablet

# ATI-450: Single and Multiple Ascending Dose Trial





# ATI-450 Development

## Rheumatoid Arthritis Phase 2 Clinical Trial

- ~ 20 patients Active Disease
- 12 wks: high dose v placebo
- Assess CRP dynamics
- Clinical Disease Activity
- MRI: wrist synovitis

Q1-Q3 2020

## Establish Principle

- Demonstrate proof of concept

CAPS

Inflammatory Bowel Disease

Psoriatic Arthritis

Hidradenitis Suppurativa

Psoriasis

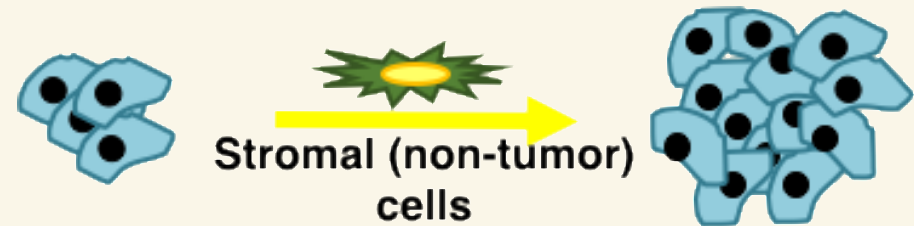
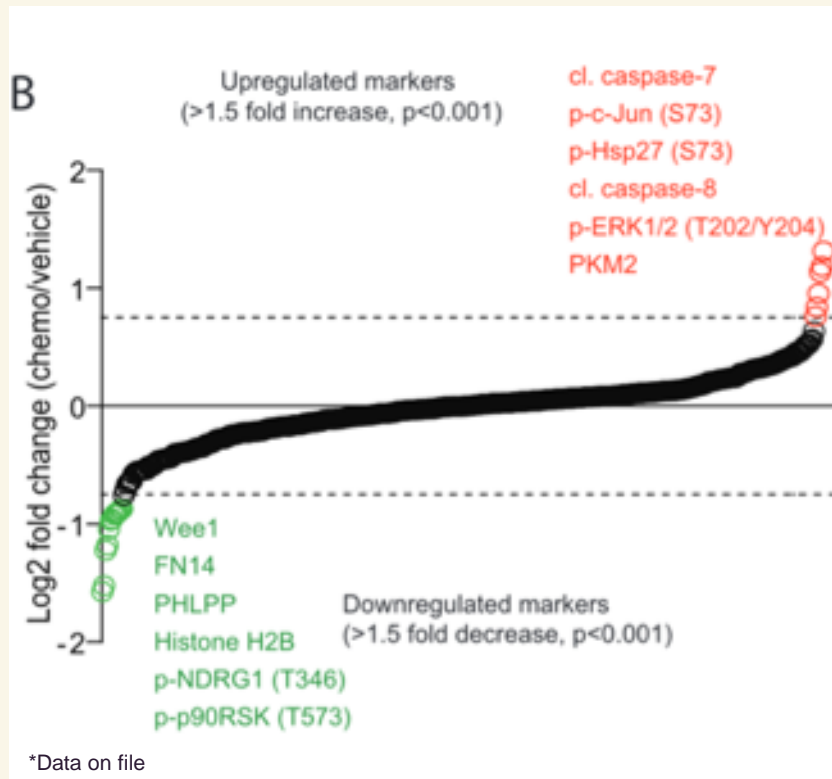
Pyoderma Gangrenosum

Rheumatoid Arthritis

# ATI-450: MK2 inhibitor in Oncology

(an investigational compound)

# ATI-450 in Oncology – Dual Mechanisms



## Breast Cancer

- Stromal cells secrete MK2-dependent inflammatory cytokines
- Cytokines drive tumor proliferation and inhibit function of immune cells
- MK2 Inhibition broadly blocks tumor growth

## Pancreatic Cancer

- Chemotherapy induces kinase targets (figure below) which can prevent apoptosis
- Inhibition of MK2 synergizes with chemotherapy-induced apoptosis

# ATI-450 in Oncology – Aclaris Strategy

- Preclinical studies suggest MK2 inhibition may be functioning in two ways:
  - Impact on the tumor microenvironment (TME) resulting in diminished production of inflammatory cytokines by stromal cells
  - Synergy with chemotherapeutic agents that induce tumor cell apoptosis
- Collaborate with oncology researchers to study Aclaris MK2 inhibitors in:
  - *In vitro* cell culture
  - Human cell line xenografts
  - Patient-derived xenografts
  - Syngeneic tumor cell models
  - Autochthonous mouse models
  - Metastasis models
  - Combination studies with standard-of-care drugs (SOC)
- Primary collaborators at Washington Univ. School of Med
  - Sheila Stewart, Professor, Oncology Division
  - Kian Lim, MD, PhD, Ass't Professor, Oncology Division

# Inhibiting the Stromal MK2 Pathway May Limit Breast Cancer Metastases and Chemotherapy-Induced Bone Loss

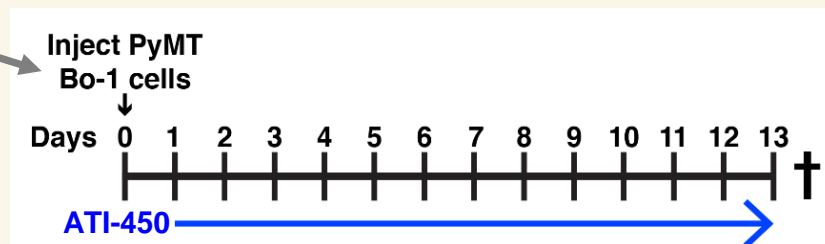
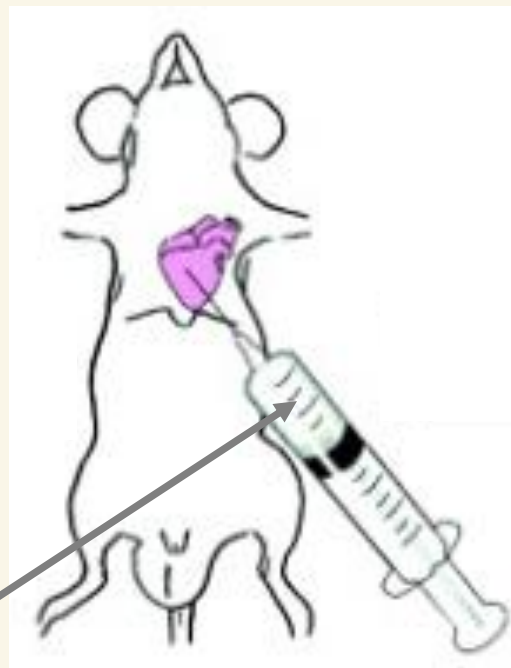
Sheila Stewart Ph.D., Washington University School of Medicine



# Modeling Bone and Visceral Metastasis in the Mouse

- 70% of all metastatic breast cancer patients harbor bone metastasis<sup>1</sup>
- Patients with bone metastases suffer numerous co-morbidities including significant risk for bone fractures<sup>1</sup>
- 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<sup>1</sup>
- Bo-1 PyMT metastatic breast cancer cell line<sup>2</sup>

## Intra-cardiac tumor cell injection model



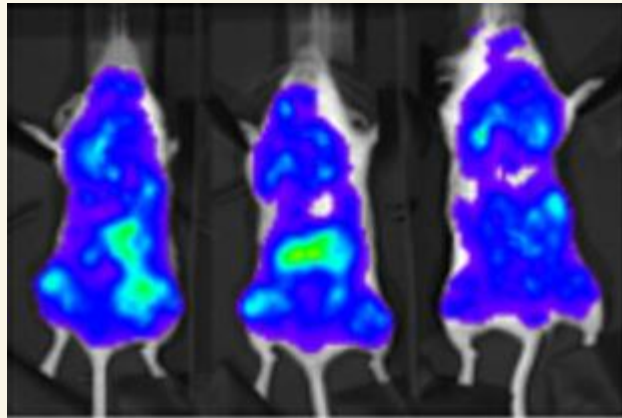
<sup>1</sup> Murali et al. 2018. Inhibition of the stromal p38MAPK/MK2 pathway limits breast cancer metastases and chemotherapy-induced bone loss. Cancer Res 78(19):1

<sup>2</sup> Su et al\_2016. Antagonizing integrin  $\beta 3$  increases immunosuppression in cancer. Cancer Res 76(12):3484

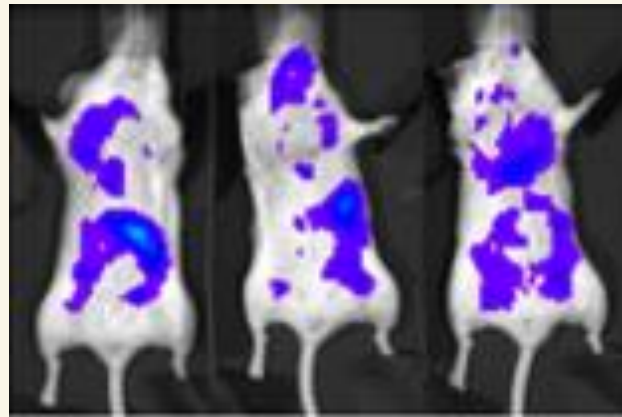
# Mouse Model: ATI-450 Reduces Visceral Organ Tumor Burden

Intra-cardiac tumor cell injection model (mouse)

Day 13 Visceral Tumor Burden



Vehicle



ATI-450

## ATI-450

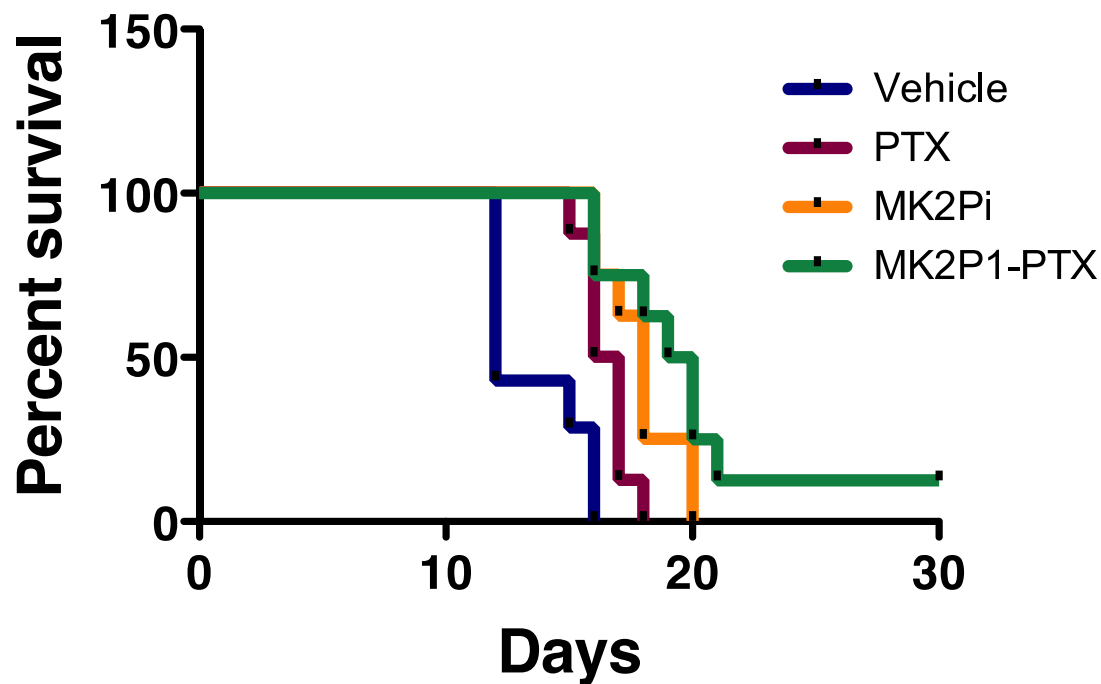
- Reduces metastatic outgrowth in visceral organs and bone
- Extends survival, both as monotherapy and in combination with Paclitaxel



# Mouse Model: ATI-450 and Paclitaxel (PTX) Increases Overall Survival

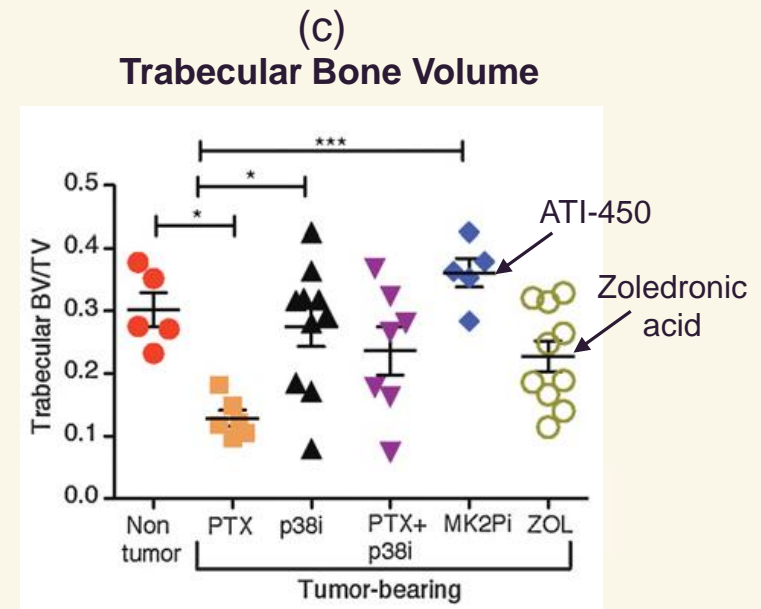
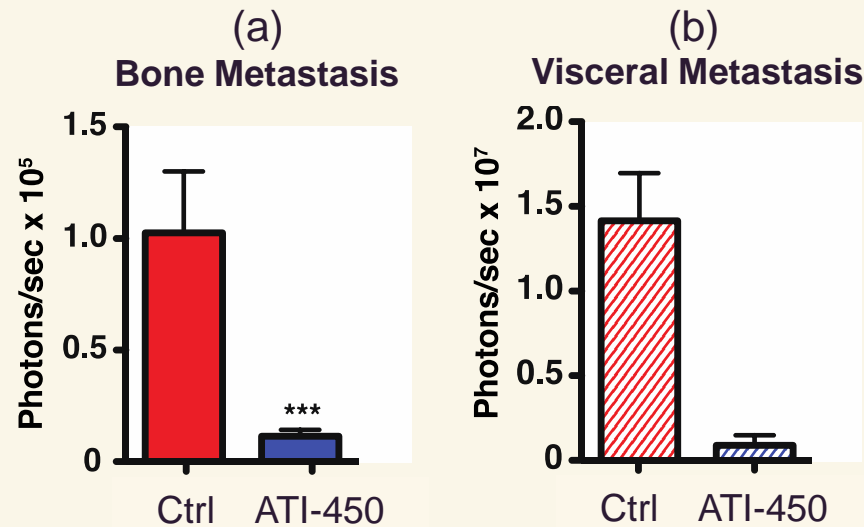
Intra-cardiac tumor cell injection model (mouse)

PTX plus ATI-450 extends survival vs. single arm treatments  
**Importantly** these agents are not antagonistic in mouse model, as PTX is SOC



# Mouse Model: ATI-450 Reduces Metastases *and* Preserves Bone

Intra-cardiac tumor cell injection model (mouse)



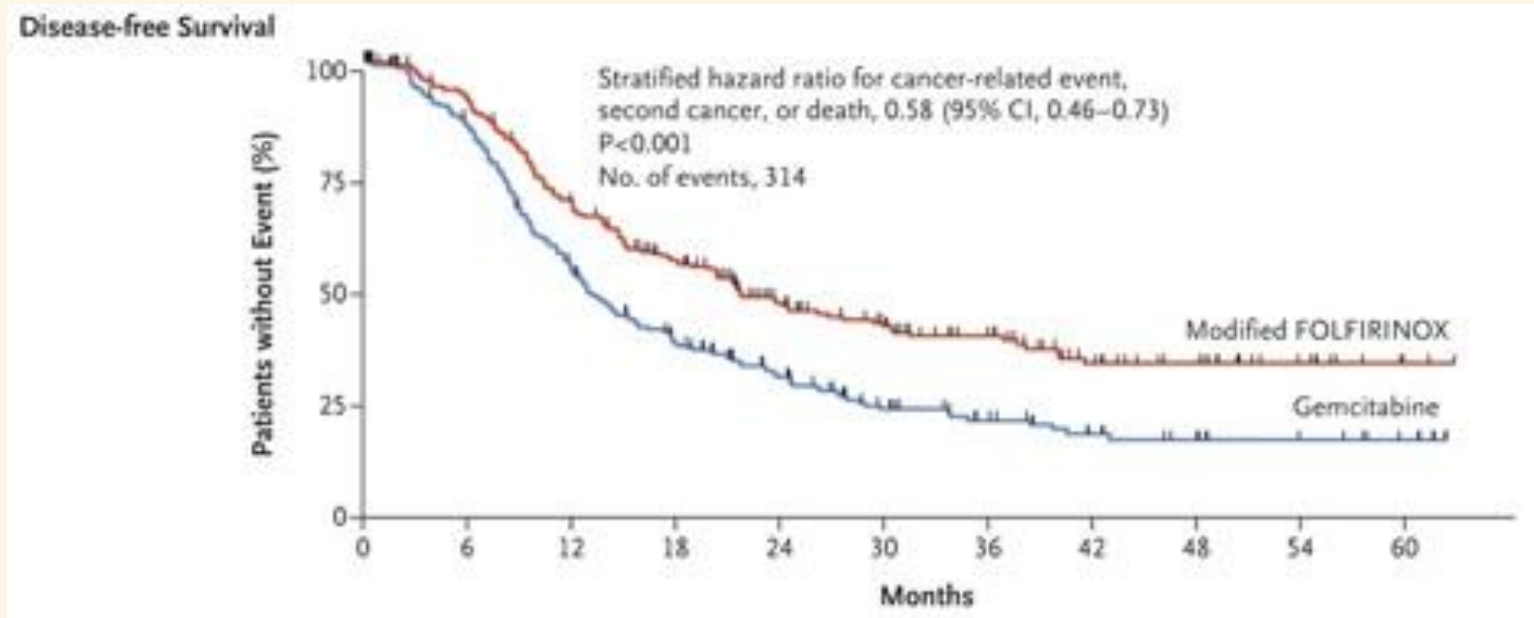
MK2Pi = MK2 pathway inhibitor, ATI-450  
p38i = global p38 MAPK inhibitor, CDD-111

**(a), (b) ATI-450 (MK2Pi) significantly reduces bone and visceral metastases in mice**  
**(c) ATI-450 preserves bone quality - as well as or better than - zoledronic acid (ZOL) and better than paclitaxel (PTX)**

# Inhibiting the MK2 pathway Inhibits Tumor Growth in Mouse Models of Pancreatic Ductal Adenocarcinoma (PDAC)

Kian Lim M.D./Ph.D., Washington University School of Medicine

# ATI-450 Pancreatic Cancer Update

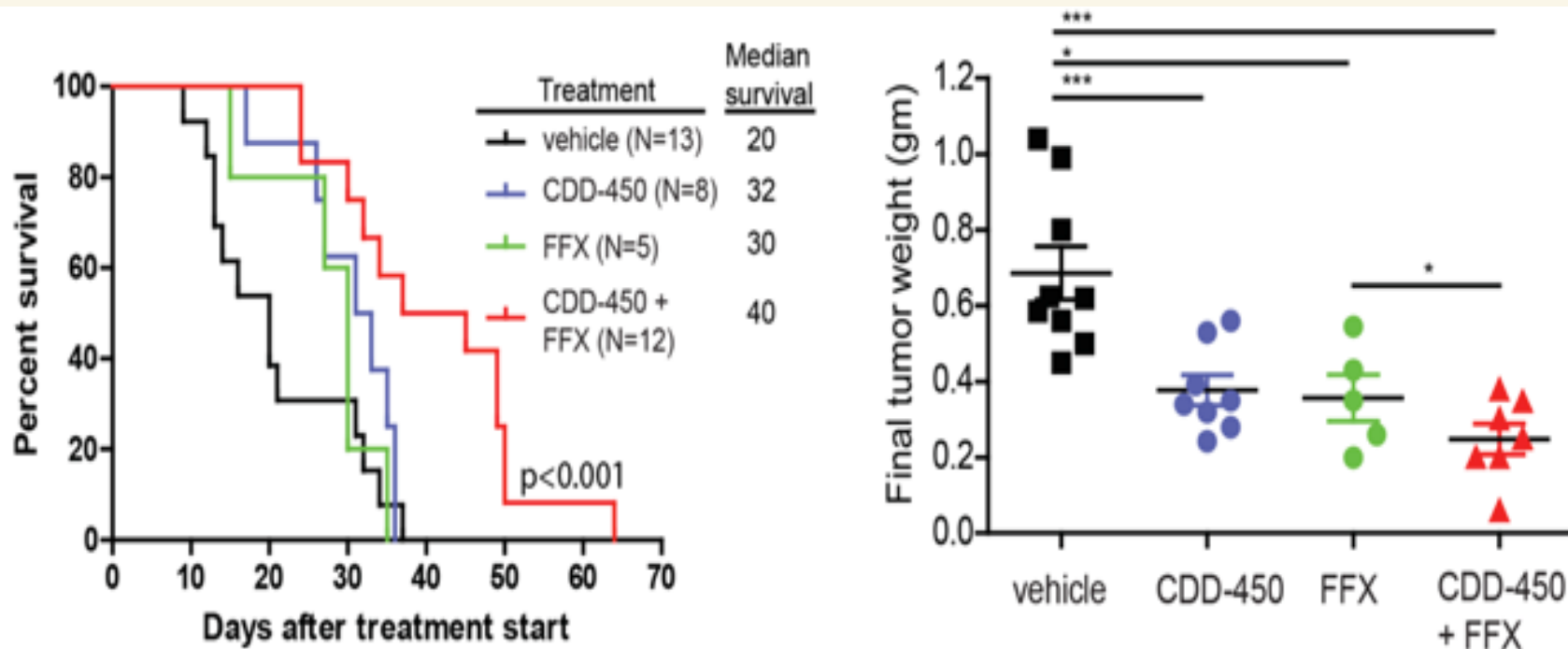


- SOC for PDAC is switching from gemcitabine to FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, oxaliplatin)<sup>1</sup>
- Regimen has high toxicity, thus additional agents must be well tolerated and overcome resistance mechanisms
- Irinotecan is the main driver of cellular stress/induced apoptosis - resistance to this stress appears to involve MK2
- Hypothesis: Will reduced dose FOLFIRINOX plus MK2 inhibition with ATI-450 improve survival and reduce toxicity?

# ATI-450 Pancreatic Cancer Update

- Lim lab shows that chemotherapy induced stress in PDAC cells driven by irinotecan (SN38)
- SN38 activates MK2/Hsp27 pathway and blockade by MK2 RNAi or ATI-450 increases SN38 induced apoptosis
- ATI-450 does not inhibit tumor growth *directly*, does suppress tumor growth *in vivo* (sc models) – move to “gold standard” KPPC model
- KPPC model:<sup>1</sup>
  - Cre promoter drives expression of the Kras G12D oncogene
  - KPPC mice have mutations in both alleles of p53 (the 2 P's).
- In the KPPC mouse model, high dose FOLFIRINOX consists of:<sup>1</sup>
  - 5FU 50mg/kg
  - Irinotecan 6.7mg/kg
  - Oxaliplatin 35mg/kg
- Low dose FOLFIRINOX is 1/2 the high dose for each component

# Combination of ATI-450 and Folfirinox Improves Efficacy in Autochthonous Mouse Model of Pancreatic Cancer (KPPC)



- Combination of ATI-450 plus low dose FOLFIRONOX improves survival compared to each drug alone in autochthonous mice
- Data supports the investigation of the addition of ATI-450 to FOLFIRINOX in patients

# Cancer: Next Steps

**ATI-450 data for MK2 inhibition in breast and pancreatic tumor mouse models has resulted in robust interest in clinical trials both as monotherapy and in combination with current standard of care**

## **Ongoing:**

- Pancreatic Cancer Models (Laboratory of Dr. Kian Lim, MD, PhD)
  - Human PDX models – monotherapy vs. combo with FOLFIRINOX
  - KPPC Model - monotherapy vs. combo with FOLFIRINOX (cont'd)
  - Metastasis model with intrasplenic injection of KPC tumor cells
  - Immune profiling of pancreatic tumors (Dr. David DeNardo, PhD)
- Breast Cancer Models (Multiple laboratories)
  - Human PDX Models (Dr. Cynthia Ma, MD, PhD)
  - Resection/metastasis model (Dr. Kathy Weilbaecher, MD)
  - Intracardiac model: monotherapy vs. combo with zoledronic acid (Dr. Sheila Stewart, PhD)
  - Immune profiling of breast tumors (Dr. David DeNardo, PhD)
- Discussions with clinical trial investigators
- Consideration of proof of principle clinical studies



# MK2 inhibitor ATI-450 Summary

- Novel mechanism designed to block inflammation
  - Multiple inflammatory cytokines impacted
  - Key RA inflammatory cell types impacted
  - Lock MK2 in a catalytically inactive state – a unique MOA
  - Broad IP issued or filed
- Oral option for numerous diseases currently treated by biologics
  - Robust efficacy in a range of inflammation and cancer models
  - Safety and pharmacology studies with acceptable profiles to support clinical trials (i.e. bioavailability, half-life, robust safety margins)
- IND open and Phase I study underway
- Proof of concept in RA trial to begin first half 2020
- Other indications under consideration

EMPOWERING PATIENTS THROUGH  
**REVELATIONARY**  
SCIENCE

**ATI-1777: Soft, Topical  
JAK1/3 Inhibitor**  
(an investigational compound)



# Rationale for a “Soft” Topical JAK Inhibitor to Target AD

To deliver topical therapy for atopic dermatitis (AD) in a way that meets the medical, aesthetic, and compliance needs of patients and physicians

## Desirable Drug Properties:

- Efficacy which will at least be as good as topical competitors and a differentiated safety profile
- Minimize the toxicity of JAK2 inhibition
- Minimize systemic immunosuppression
- Formulation which is differentiated from other topical therapies

# Why a “Soft” Topical; why Atopic Dermatitis?

- Aclaris’ goal is to deliver a “soft” topical JAK inhibitor to achieve efficacy in skin while minimizing systemic exposure
  - A soft drug is designed to be rapidly metabolized to an inactive form
- AD is the primary clinical target
  - There is an unmet need for effective and safe topical treatment for AD
    - particularly for children
  - Systemic and topical JAK inhibition has demonstrated promising results in clinical trials for treating pruritus and inflammation in AD<sup>1</sup>
  - Topical dosing to intact skin is typically associated with low plasma drug levels. However, in AD, a compromised skin barrier means that a topically dosed JAK inhibitor might result in pharmacologically active systemic drug levels

# Designing a Drug Physicians and Patients May Prefer

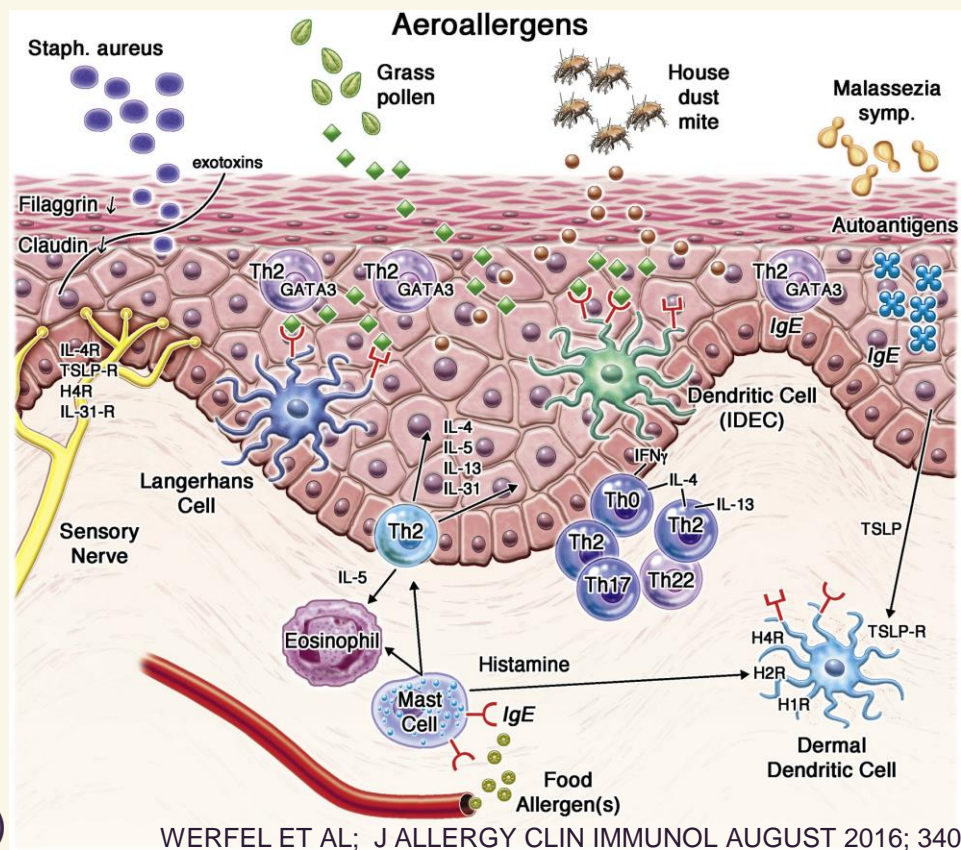
Aclaris is developing novel “soft” JAK inhibitors for topical use

- Potent in enzyme and cell assays
- JAK1/3 selective
- Favorable physicochemical properties for a topical product
- Designed to be active in skin but rapidly metabolized once it reaches the systemic circulation
- ATI-1777 is our lead candidate for the potential treatment of AD
  - Solution formulations are amenable to either direct topical or spray application
  - IND-enabling activities underway
  - GMP drug substance completed and ready



# Oral and Topical JAK Inhibitors are Clinically Effective in AD

- Rates of AD are around 30% in the most developed nations and exceed 10% in many countries. Worldwide cumulative prevalence of 15-20%<sup>1</sup>
- AD strongly driven by Th2 cells → IL-4/13
- IL-4R uses JAK1/3, IL-13R uses JAK1/2
- Orally dosed baricitinib (JAK1/2); upadacitinib (JAK1); and PF-04965842 (JAK1) show efficacy in Phase 2/3 AD trials<sup>2</sup>
- Topically dosed tofacitinib (JAK1/3), ruxolitinib (JAK1/2), delgocitinib (JAK1/2/3) in clinical trials
- Dupixent® (dupilumab, Sanofi-Regeneron) antibody blocks both IL-4/13



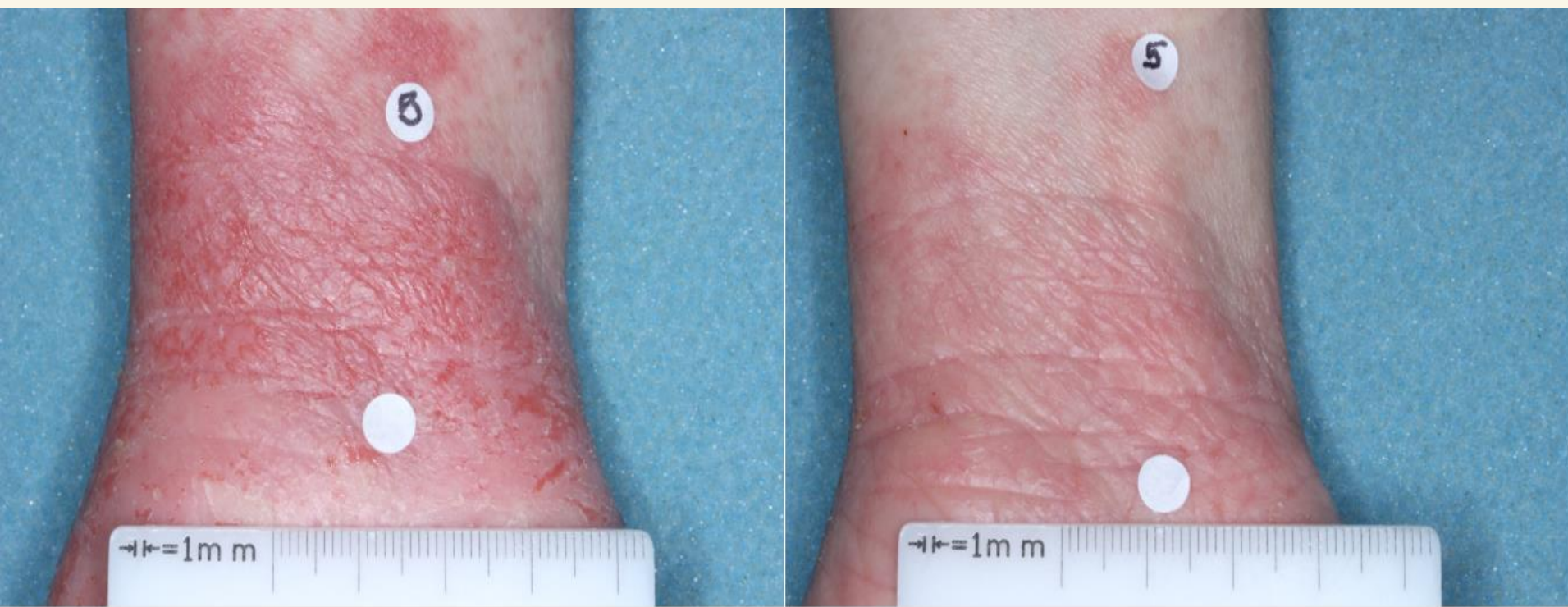
Topical ATI-1777 has a high probability of demonstrating efficacy and safety in AD

<sup>1</sup> James W, et al Andrew's Diseases of the Skin Clinical Dermatology, 2011, 11<sup>th</sup> edition

<sup>2</sup> <https://news.abbvie.com/news/abbvie-presents-new-late-breaking-phase-2b-data-on-upadacitinib-in-atopic-dermatitis-at-2018-american-academy-dermatology-annual-meeting.htm>; <https://investor.lilly.com/news-releases/news-release-details/lilly-announces-top-line-phase-3-results-baricitinib-patients>; <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-positive-top-line-results-from-phase-3-study-of-investigational-oral-jak1-candidate-abrocitinib-pf-04965842-in-patients-aged-12-and-older-with-moderate-to-severe-atopic-dermatitis>

# ATI-502-AD-201 Topical: Pilot Study of Topical JAK1/3 Inhibitor

- ATI-502 Topical Solution, 0.46% (not soft)
- Patients with Moderate to severe AD: Physician Global Assessment (PGA) 3/4
- 28 days open label treatment
- 17 completers: 7/17 (41.2%) achieved  $\text{PGA} \leq 1$  (at least 2-point change)

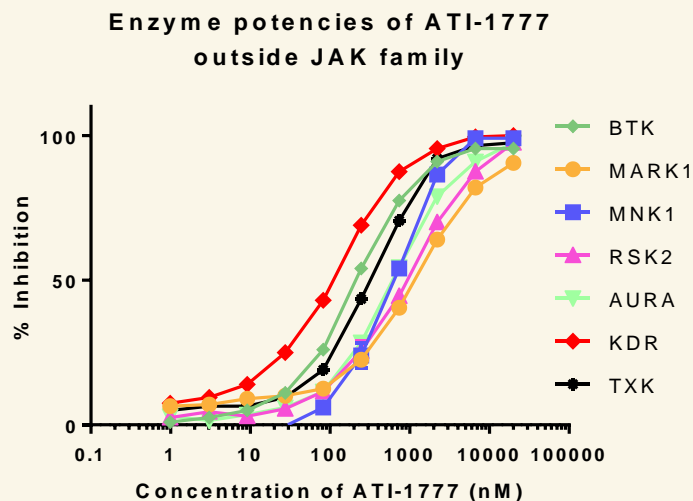
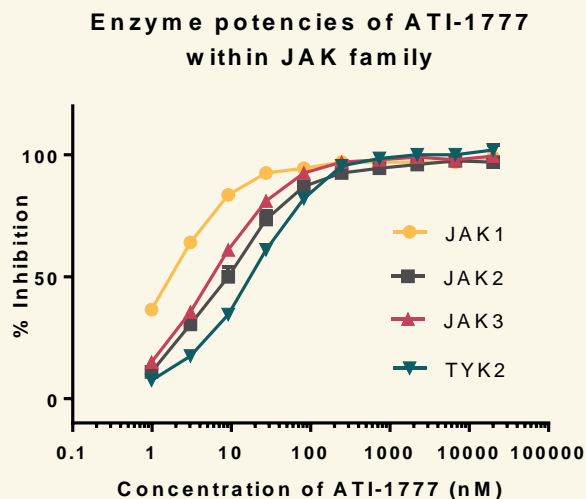




# Designing a Better Topical Drug for Atopic Dermatitis

- ✓ Design potent/selective JAK enzyme inhibitors
- ✓ Confirm cellular potency and selectivity
- ✓ Design compounds to be metabolically unstable
- ✓ Create patient-friendly formulation
- ✓ Design topical pharmacodynamic model
- ✓ Demonstrate minimal systemic exposure
  - Evaluate in early clinical studies

# ATI-1777: Enzymatic Potency and Selectivity



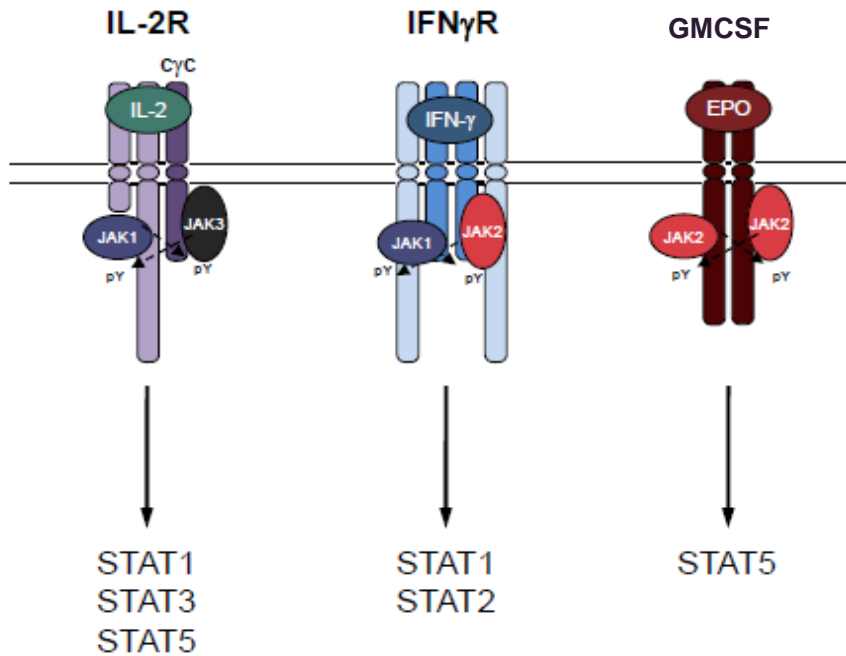
**Enzyme Potencies (IC<sub>50</sub>, nM)**

JAK1	JAK2	JAK3	TYK2	BTK	MARK1	MNK1	RSK2	AurA	KDR	TXK
<b>1.5</b>	<b>7.1</b>	<b>3.8</b>	<b>19</b>	210	1250	584	1050	641	127	351

The kinome selectivity of ATI-1777 was evaluated against 194 kinases as 5 $\mu$ M at LifeTech. IC<sub>50</sub> values were generated at K<sub>m</sub> ATP concentrations on those kinases that inhibited  $\geq$ 80% at 5 $\mu$ M.

ATI-1777 is highly selective for the JAK family over other kinases in the kinome

# Cellular JAK/STAT Assays



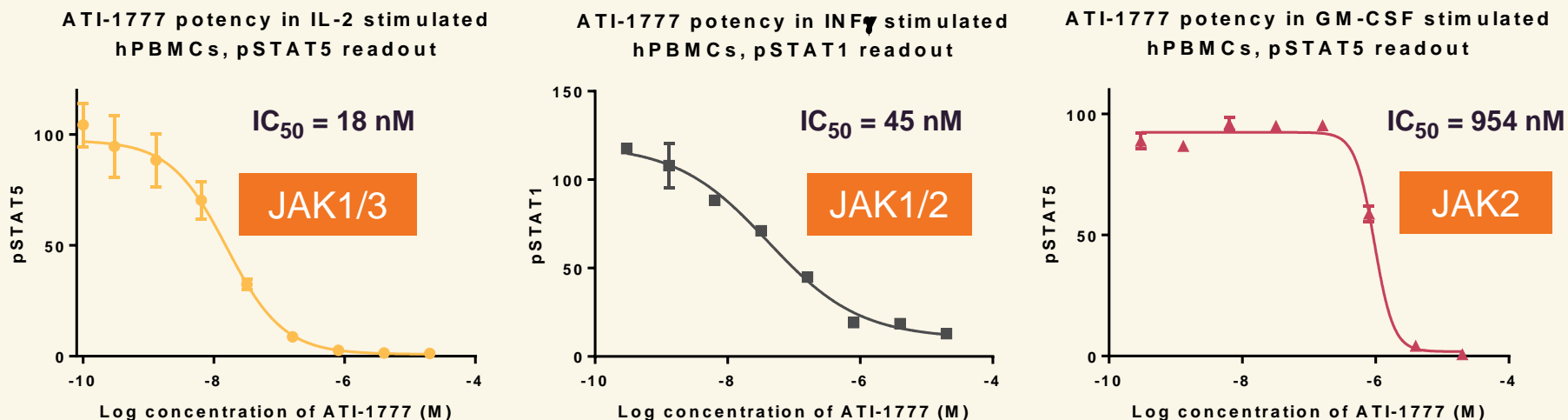
Cytokine	JAKs	STAT
IL-2 / IL-15	JAK1/3	STAT5
IFN $\gamma$	JAK1/2	STAT1
GM-CSF	JAK2	STAT5

Human peripheral blood mononuclear cells stimulated by different cytokines, signal through different pairings of JAK kinases to phosphorylate downstream signal transducers and activators for transcription (STATs)

- IL-2 stimulation requires JAK1 and JAK3 to phosphorylate STAT5
- IFN $\gamma$  stimulation requires JAK1 and JAK2 to phosphorylate STAT1
- GM-CSF stimulation requires only JAK2 to phosphorylate STAT5

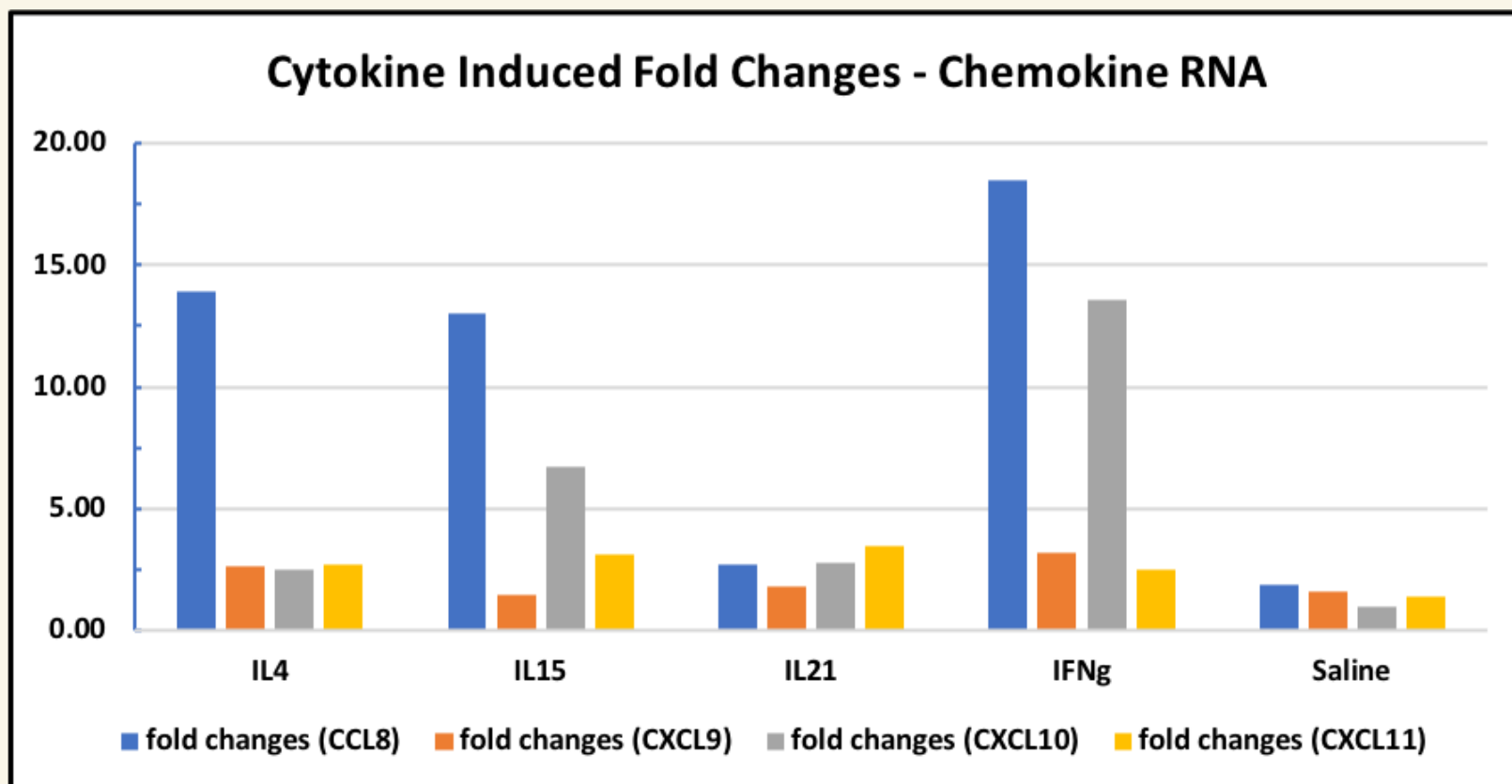
# ATI-1777: Cellular Potency and JAK Selectivity in Human Cells

Functional selectivity assessed by stimulating hPBMCs with IL-2 (STAT5), IFN- $\gamma$  (STAT1), and GM-CSF (STAT5) - measuring IC<sub>50</sub>s for inhibiting P-STAT generation



In human cells, ATI-1777 exhibited selectivity for JAK1/3 over JAK2 signaling

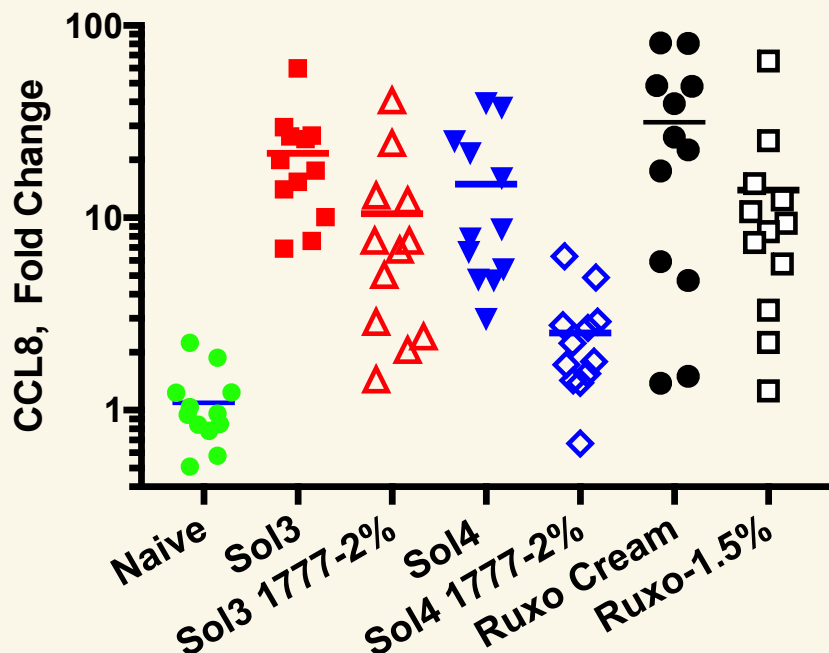
# Porcine Model: Building a Robust Topical Pharmacodynamic Model



- Compound in topical formulations applied to skin
- JAK-dependent cytokines injected intradermally
- Biopsies harvested/RNA prepared
- Chemokine genes robustly induced (CCL8, CXCL10)
- ATI-1777 in various formulations blocks induced RNA

# Porcine Model: ATI-1777 in Two Formulations Blocked IL-15 Induced CCL8

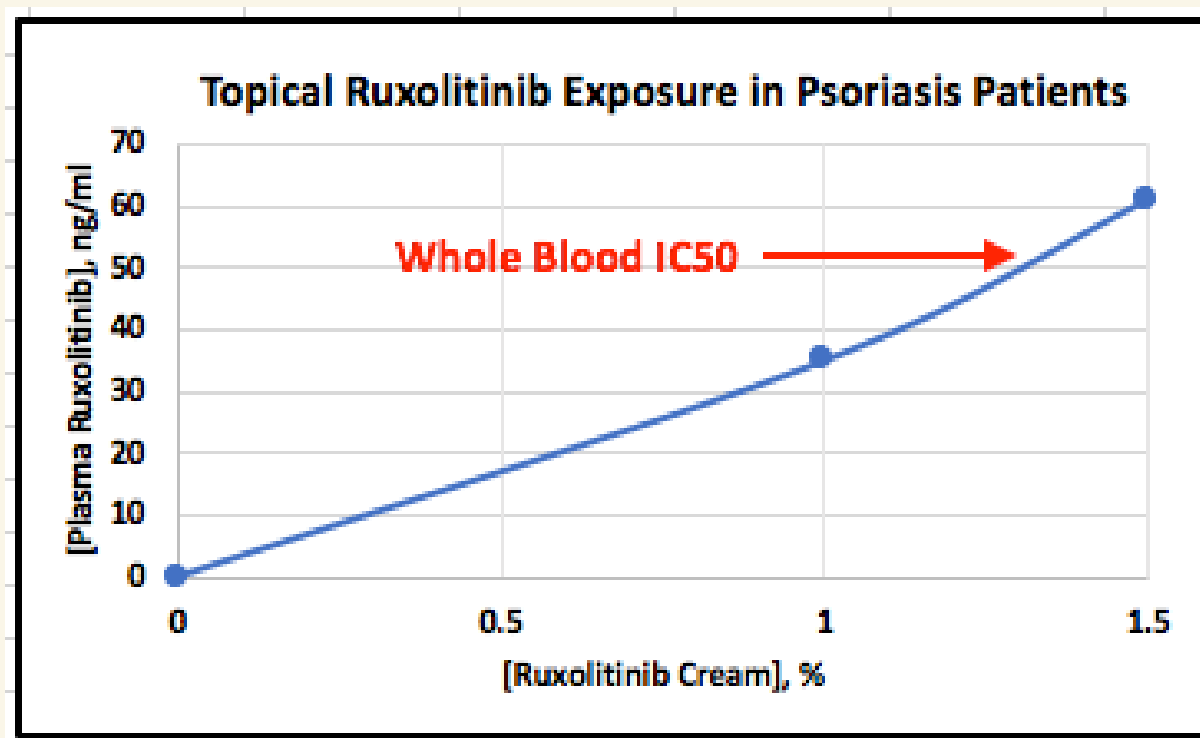
PD Effects of ATI-1777 in Pigs



- After 1 hour, application sites were injected with porcine IL-15 (JAK1/3 dependent cytokine)
- RNA prepared from biopsies and qPCR analysis performed to measure levels of induced CCL8 mRNA
- Fold change in CCL8 RNA expressed relative to levels in naïve skin (graph)
- Significance and % decrease expressed relative to respective placebo formulations (table)
- Prototype formulations perform as well - or better than - clinically validated formulation of ruxolitinib
- Advancing Solution 4 (Sol4)

Formulation	P value	% Decrease
Solution 3	0.0460	52
<b>Solution 4</b>	<b>0.0031</b>	<b>83</b>
Ruxo Cream	0.0831	56

# Clinical Ruxolitinib Systemic Exposure After Topical Application



- In 28 day topical **BID** dosing of **patients with psoriasis** with 1.0 and 1.5% cream:
  - **Average** plasma exposures of **35 or 61 nM<sup>1</sup>**, as high as **191 nM**.
  - Ruxolitinib whole blood IC<sub>50</sub> (**red line**) is **~50 nM<sup>2</sup>** – **thus drug is not restricted to the skin after topical dosing.**

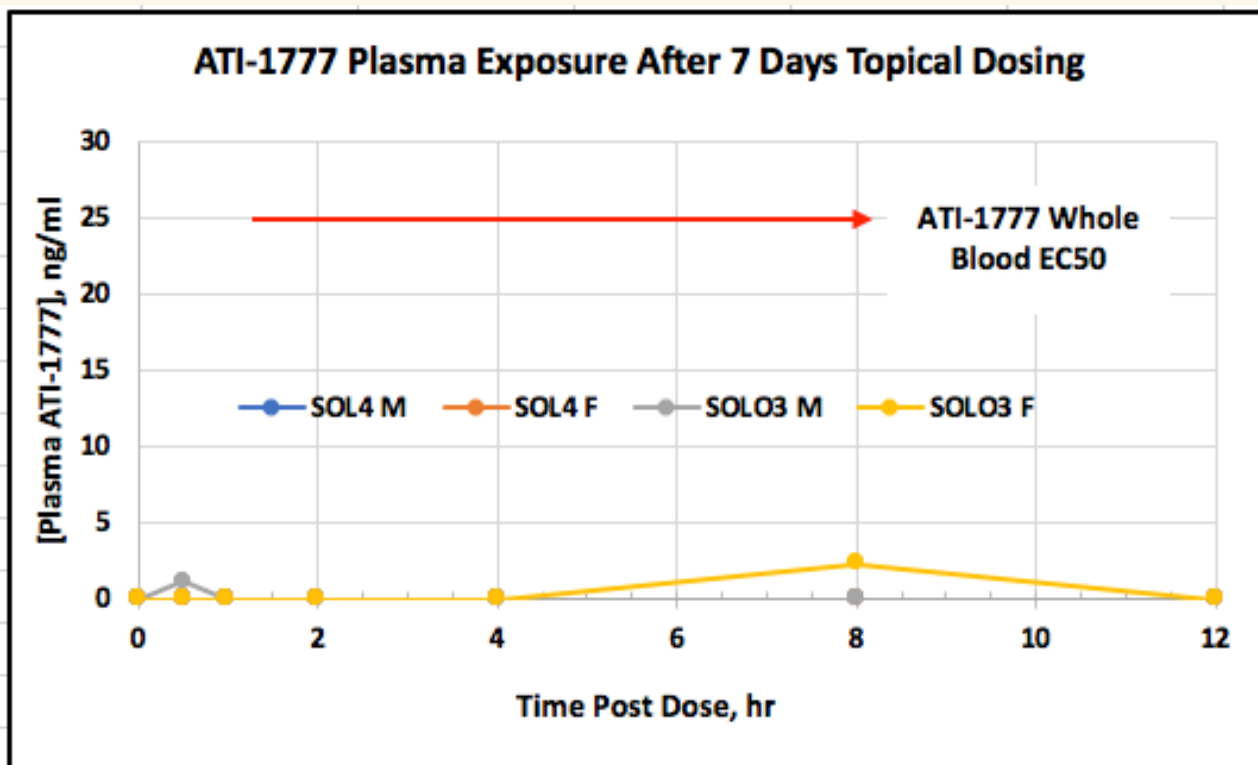
1. Downmodulation of key inflammatory cell markers with a topical Janus kinase 1/2 inhibitor. 2015. British Journal of Dermatology 173:989–997  
2. Pharmacokinetics and Pharmacodynamics of Orally Administered Ruxolitinib (INCB018424 Phosphate) in Renal and Hepatic Impairment Patients. 2013. Clinical Pharmacology in Drug Development 3:34–42



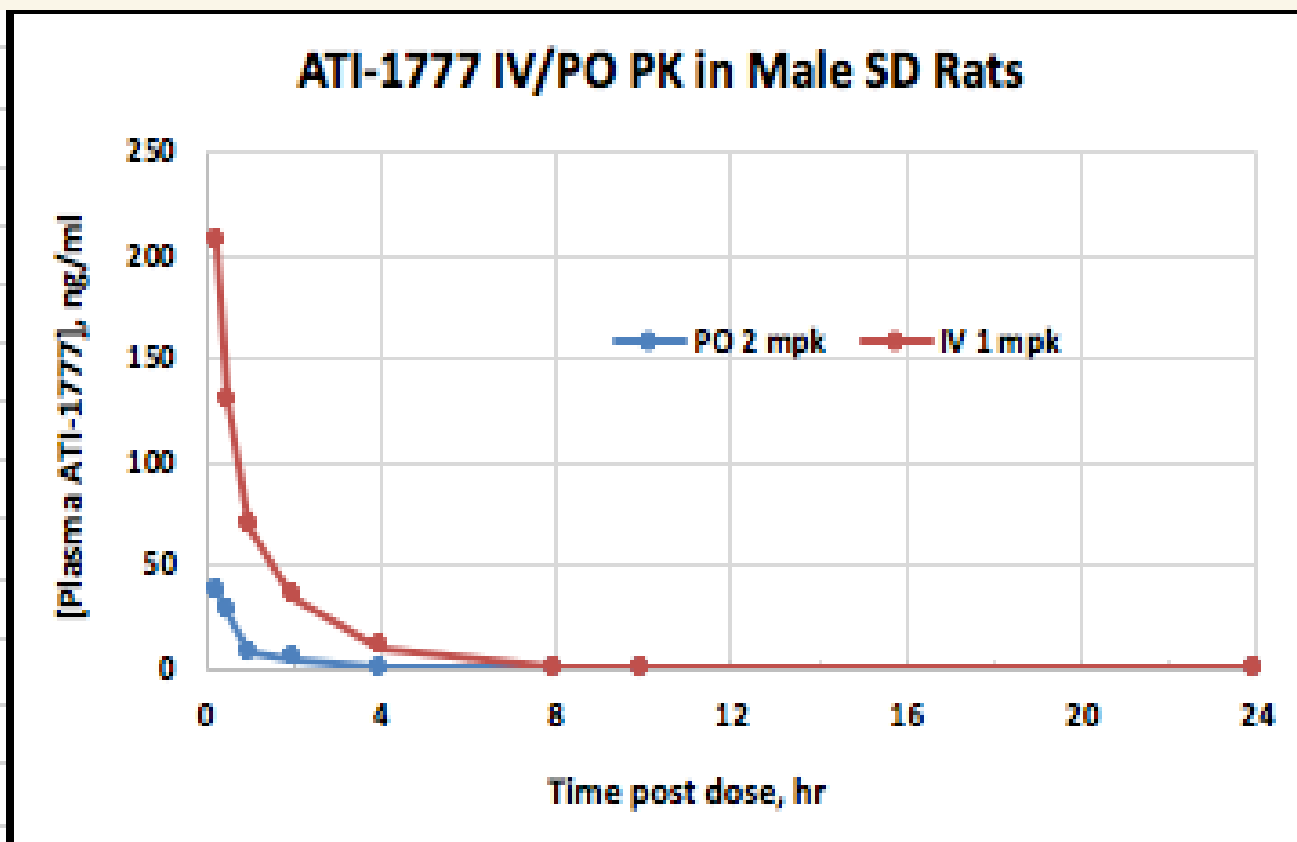
# Minipig Model: ATI-1777 Nonclinical Safety Program TK Data

## Tolerability/Toxicokinetic with 7-day dermal administration (non-GLP)

- No adverse effects noted for each of 4 tested formulations (10% BSA QD)
- Bleeds at 0.5, 1, 2, 4, 8, 12, and 24 hours post-application: Days 1 and 6
- **Most** plasma samples were **BLQ** (<0.50 ng/mL) – well below cellular IC50



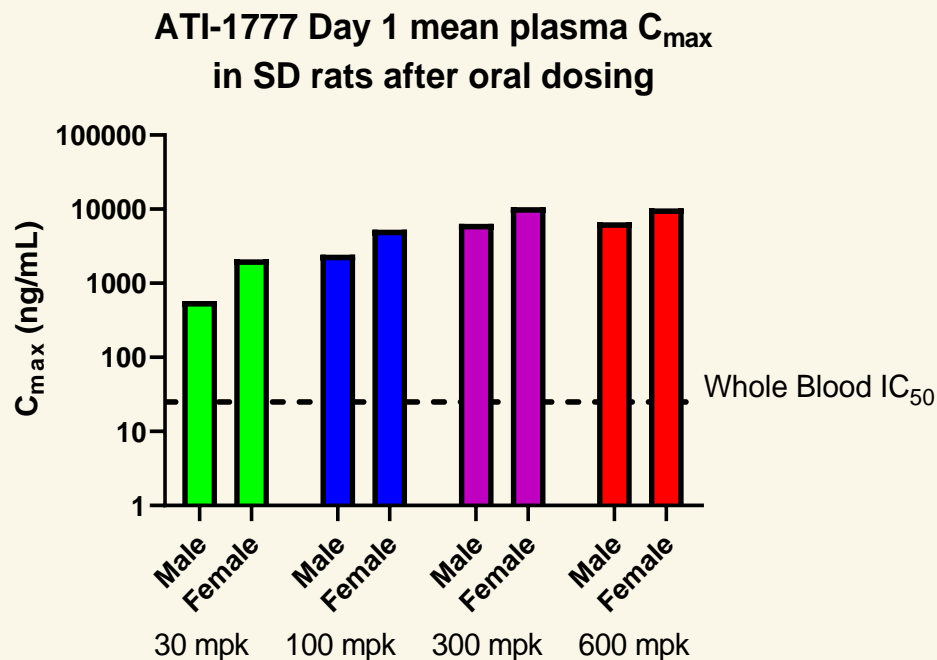
## Rodent Model: ATI-1777 *In Vivo* PK Properties



- ATI-1777 is rapidly cleared after IV administration
  - Measured clearance higher than liver blood flow (indicating extrahepatic clearance)
  - IV half life was <0.5 hr
  - Profile consistent with that of a “soft” drug

# Rodent Model: ATI-1777 Nonclinical Safety Program

## 7-Day Oral Dose-Range Finding Study in Rats (non-GLP): Toxicokinetic Parameters



### Key Findings:

- Based on the results of the 7-day oral DRF study in rats, the no-observed-adverse-effect level (NOAEL) was considered to be  $\geq 600$  mg/kg/day
- This resulted in  $C_{\max} = 7680$  ng/mL, and  $AUC_{0-t} = 42,700$  ng\*h/mL for males on Day 7, respectively

Topical administration in rodents resulted in plasma drug levels  $< 1$  ng/ml, but these orally dosed tox studies achieved  $> 7,000$  ng/ml plasma levels

# Summary of Formulation Development

- API free base selected for progression into formulation development activities
- Based on the solubility and compatibility data: creams, polyethylene glycol (PEG) based ointments, foams, gels (both aqueous and non-aqueous) and solutions were developed
- Solution 4 (SOL4), a 2 wt% (API) emollient-containing anhydrous solution, was selected for progression to 28d and FIH studies based on the following:
  - Maximum drug loading
  - Solution > Non-aqueous gel > PEG ointment > foam > creams
  - Preliminary chemical stability
  - *In vitro* permeability studies
  - Aesthetic evaluation in 62 AD patients
  - Activity in pig PD model
  - 7d toxicology studies in pigs
- FIH studies will apply the solution with a dropper applicator
- A non-aerosol spray is under consideration for Phase 2 studies

# ATI-1777: Soft Topical JAK Inhibitor Summary

- Potent inhibitor of JAK1 and JAK3
  - JAK1/3 receptor selectivity minimizes JAK2 toxicities
- Results in pre-clinical rodent and pig models
  - Topical activity demonstrated in both animal models
  - Designed for rapid metabolism to potentially minimize systemic toxicities
- Topical formulations being optimized
  - To be delivered in a differentiated, patient-friendly formulation
- GMP synthesis completed
- Safety studies
  - 7-day rat oral IVT up to 600 mg/kg complete
  - 7-day dermal mini-pig complete
  - IND enabling studies in progress
  - First in Human studies planned for second half 2020

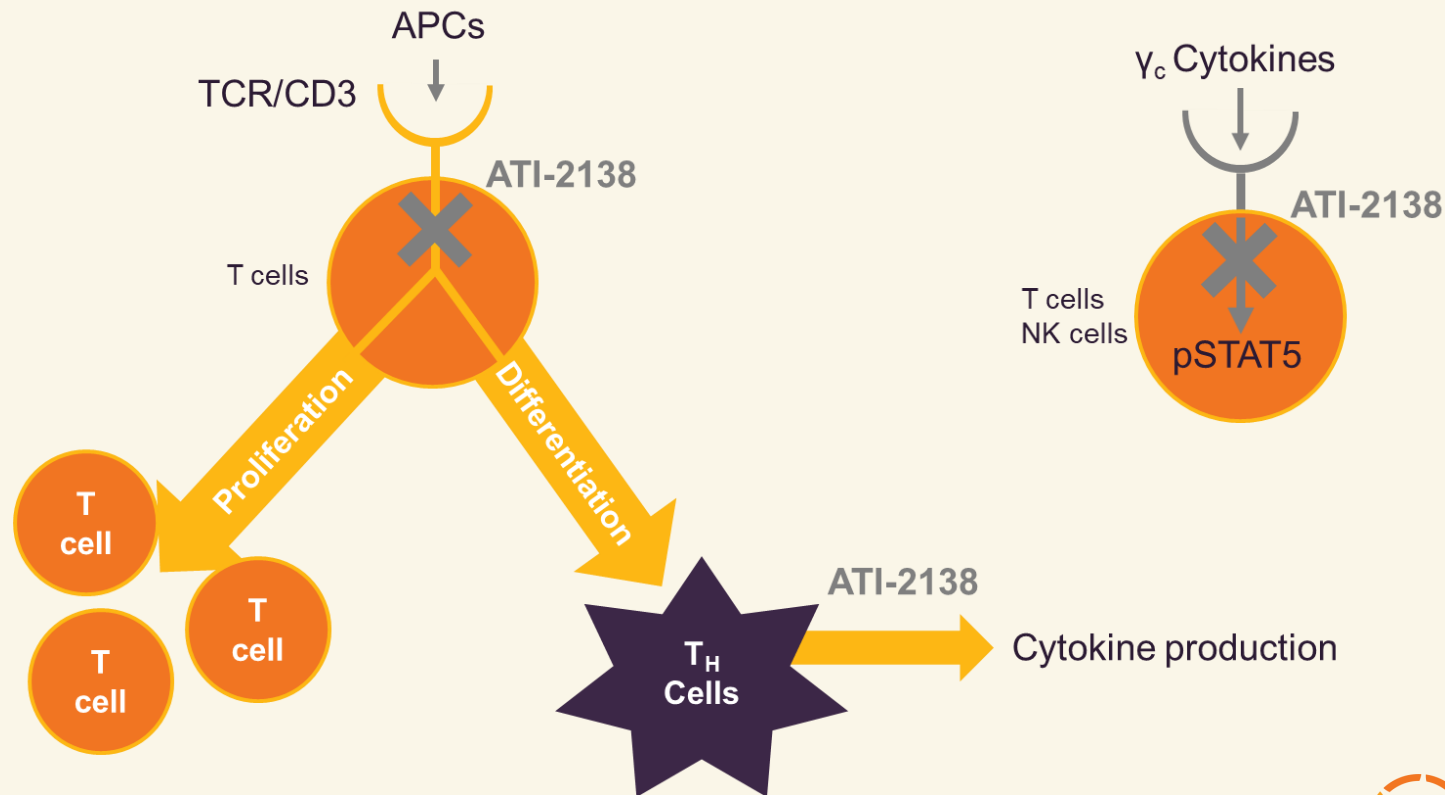
EMPOWERING PATIENTS THROUGH  
**REVELATIONARY**  
SCIENCE

**ATI-2138: ITK/TXK/JAK3**  
**Inhibitor**  
(an investigational compound)



# ATI-2138: ITK/TXK/JAK3 Inhibitor for Autoimmune Disease

- ATI-2138 is an investigational oral compound which interrupts T cell receptor (TCR) signaling and cytokine signaling in lymphocytes
- Evaluating for the potential treatment for a number of T cell mediated autoimmune diseases

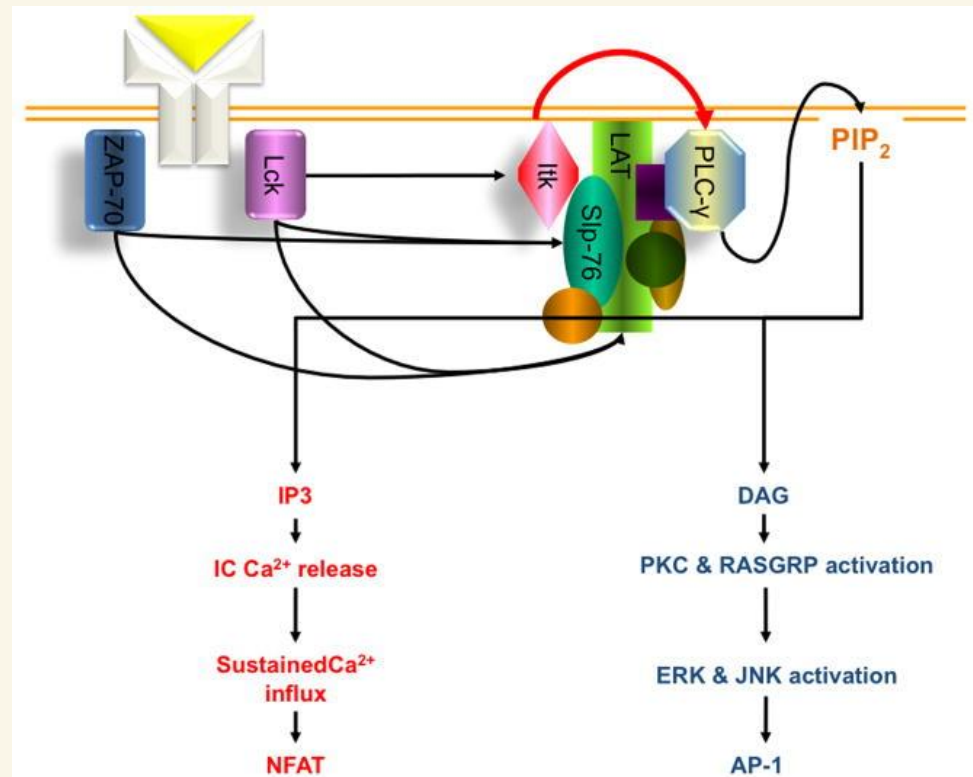




# ITK/TKX Function and Expression

- ITK and TKX are members of the TEC family of kinases
- ITK and TKX have overlapping functions
- Expression restricted to T cells, NK cells, and mast cells
- ITK and TKX are downstream of the T cell receptor
- ATI-2138 is designed to reduce T cell differentiation, proliferation and cytokine production

ITK and TKX regulates the T cell receptor



Prince, A.L. et al., *Immunological Reviews* 2009, 228 115–131

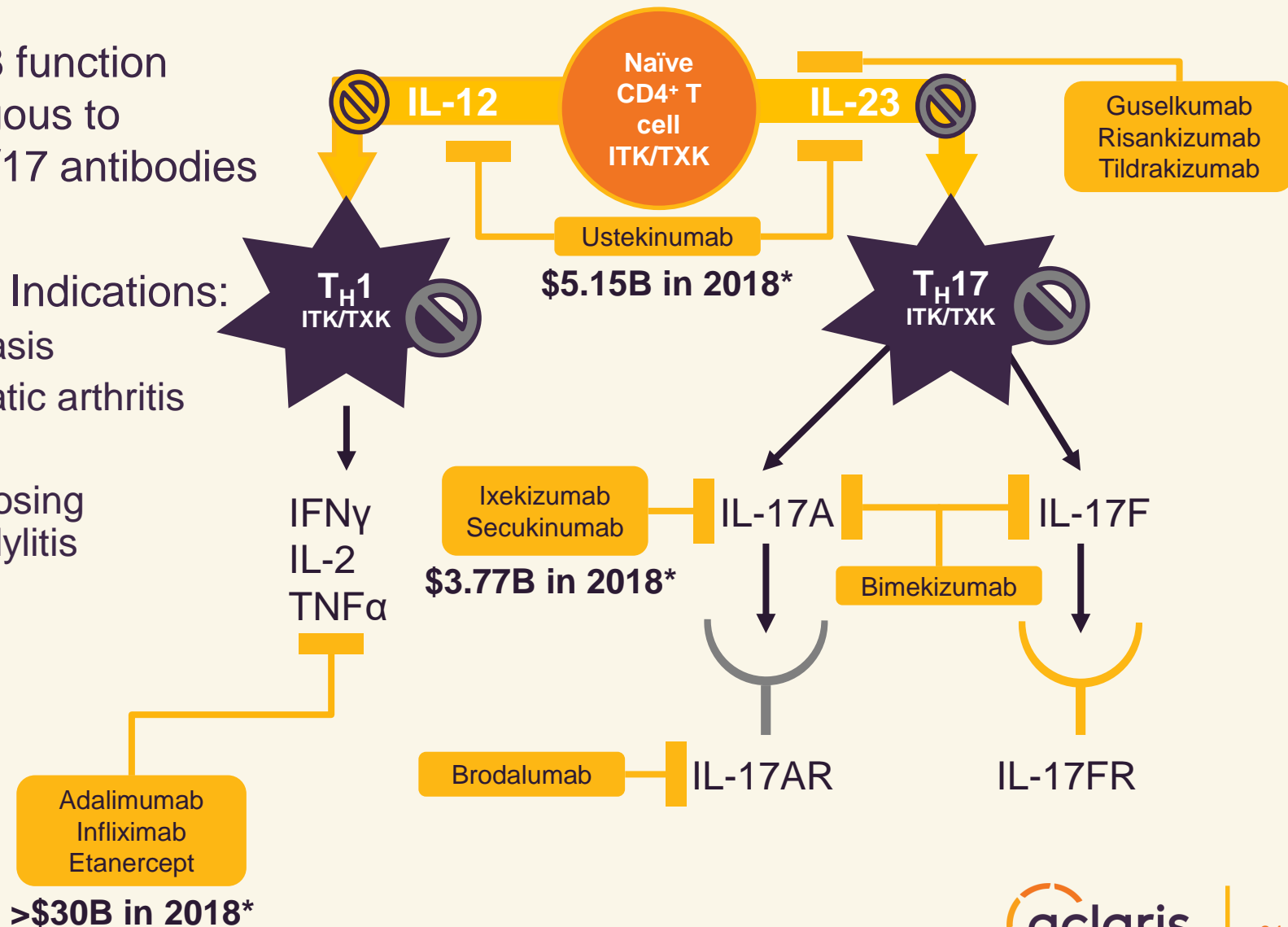
**ATI-2138 functions like cyclosporine in reducing TCR signaling,  
but acts on targets restricted to lymphocytes**  
**ATI-2138 has the potential to avoid toxicities associated with cyclosporine**

# ATI-2138: Impacts Clinically Important Pathways

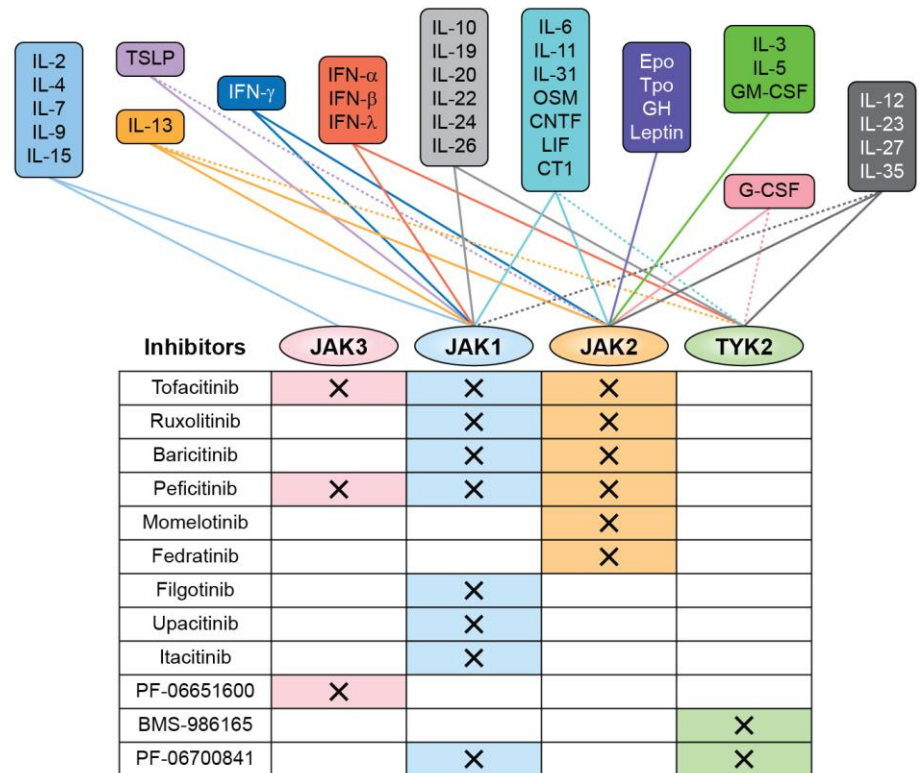
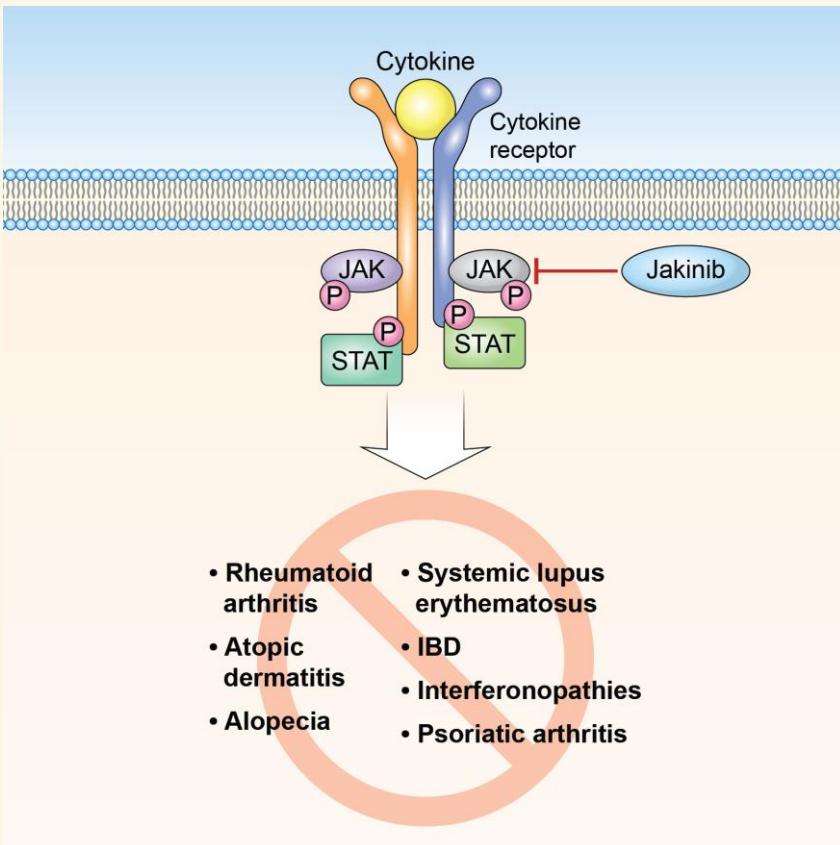
- ATI-2138 function is analogous to IL-12/23/17 antibodies

- Potential Indications:

- Psoriasis
- Psoriatic arthritis
- IBD
- Ankylosing spondylitis



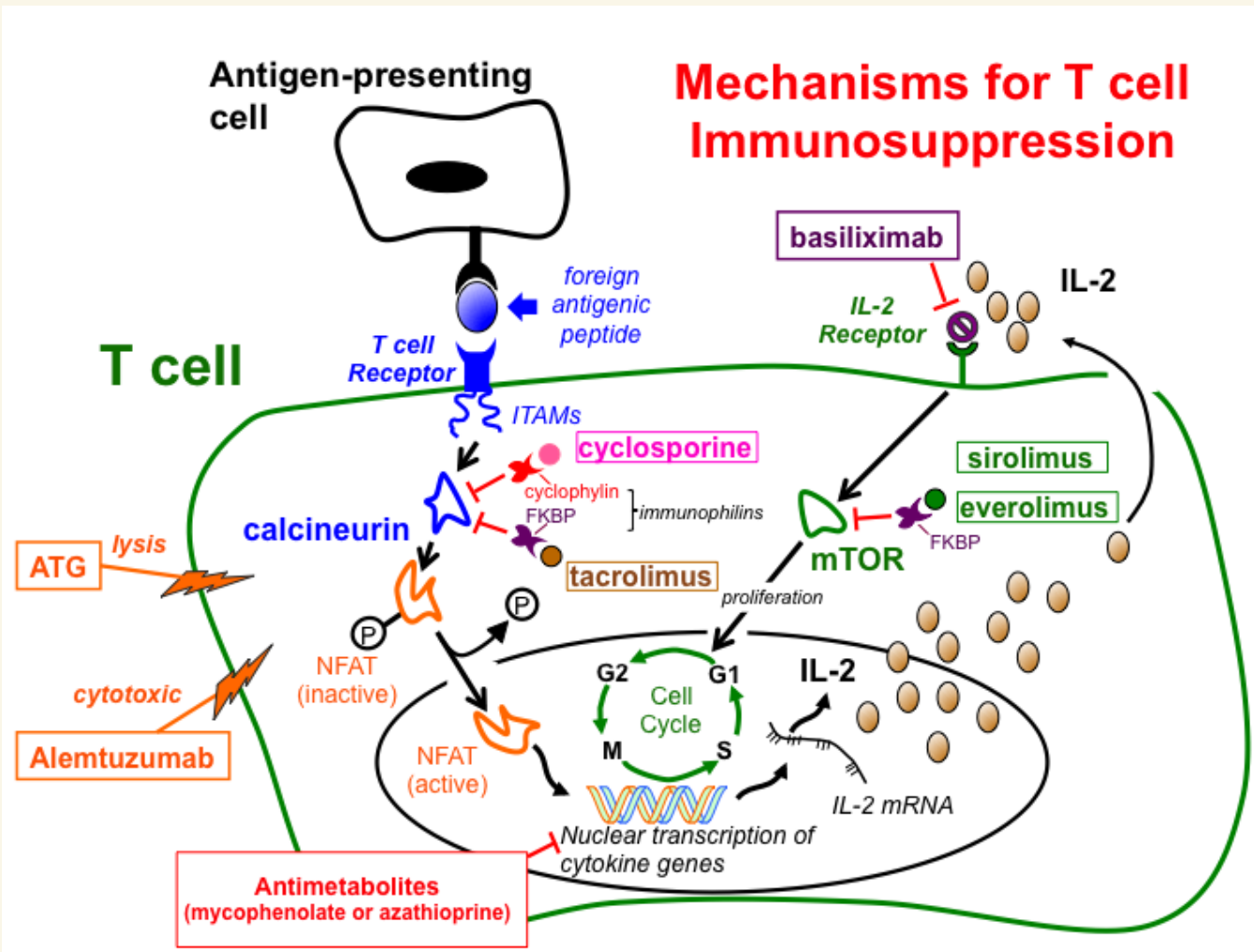
# JAK signaling and JAK inhibitors



Gadina, M. et al., *J. Leukoc Biol.*, **2018**, 104, 499

- Cytokine receptors pair with JAK kinases to phosphorylate STATs
- Multiple inhibitors of JAK kinases have been approved for and are currently in clinical trials for inflammatory diseases

# Examples from the Organ Transplant Field



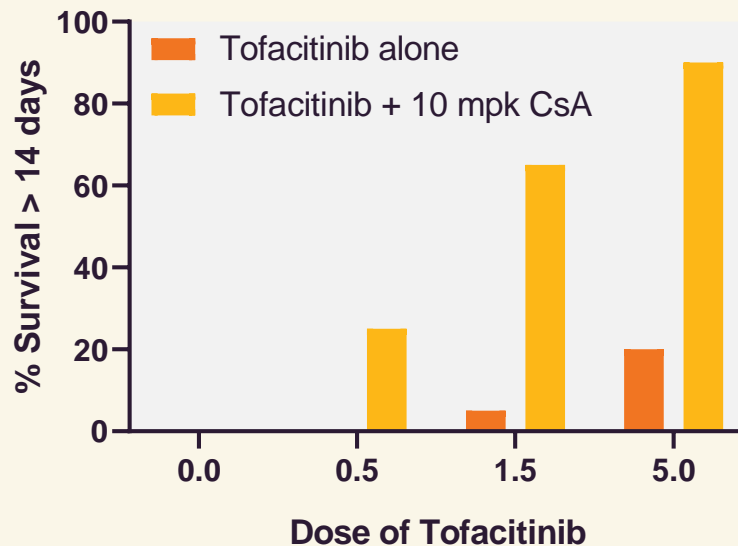
- Combination regimens are better able to block complex immunologic cascades involved with inflammatory responses, and avoid the use of higher, more toxic doses of individual drugs
- Main pathways targeted in all transplant drug cocktails are the T cell receptor (blocked with cyclosporine / tacrolimus) and IL-2R (blocked by tofacitinib or  $\alpha$ IL-2R)
- ITK/TKK inhibitors will block T cell receptor and JAK3 inhibitor will block IL-2R
- By virtue of blocking ITK/TKK and JAK3 with ATI-2138 – synergy has been demonstrated **with low dose of one drug in pre-clinical models**

Adapted from: Wood KJ, Goto R (2012): Mechanisms of rejection: current perspectives. Transplantation 93(1):1-10.

# Combination of TCR and Cytokine Signaling can Produce Synergistic Effects



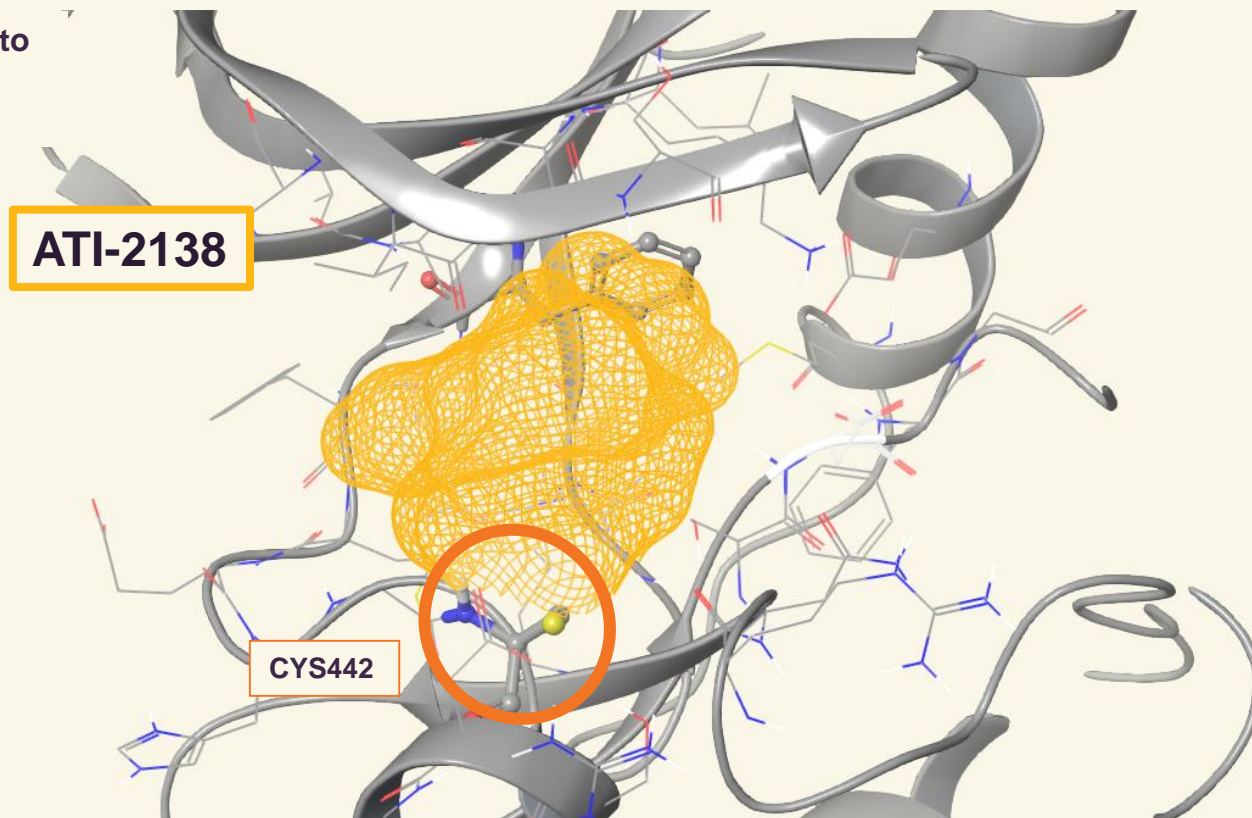
**Survival of mice after cardiac transplant**



- Tofacitinib was originally developed as a drug for transplant rejection
- The combination of tofacitinib and cyclosporine was significantly more active than either drug alone
- By inhibiting **both** the TCR and cytokine signaling pathways with the same agent greater effects may be observed than either pathway alone

# Pre-clinical Data: ATI-2138 Covalently Inhibits ITK, TXK and JAK3

ATI-2138 modeled into  
ITK kinase domain  
3QGY



- Design guided by modeling and proprietary crystal structures
- ATI-2138 was designed to interact with ATP site and covalently modify CYS
  - CYS442 in ITK
- Other oral drugs have successfully targeted this cysteine in kinases
  - Ibrutinib (BTK)
  - Afatinib, Neratinib (EGFR/Her2)
  - PF-06651600 (JAK3)



## ATI-2138: Activity in Enzyme Based Assays

Kinase	IC <sub>50</sub> (nM)	Selectivity Ratio
BLK	34	170
BMX	2.7	13.5
BTK	7	35
ITK	0.2	--
JAK3	0.5	2.5
TEC	109	545
TXK	4.8	24

- Broad panel kinase panel screening of 194 kinases at 1  $\mu$ M
- IC<sub>50</sub> values determined for kinases with >85% inhibition
- Weak potency against kinases that lack a CYS residue
  - Inhibition is reversible in these cases
- Varying potency within TEC family of kinases
  - Most potent for ITK
- Crossover onto JAK3 and which also contains a CYS residue
- *>90% of the kinases didn't give any inhibition at 1 micromolar*

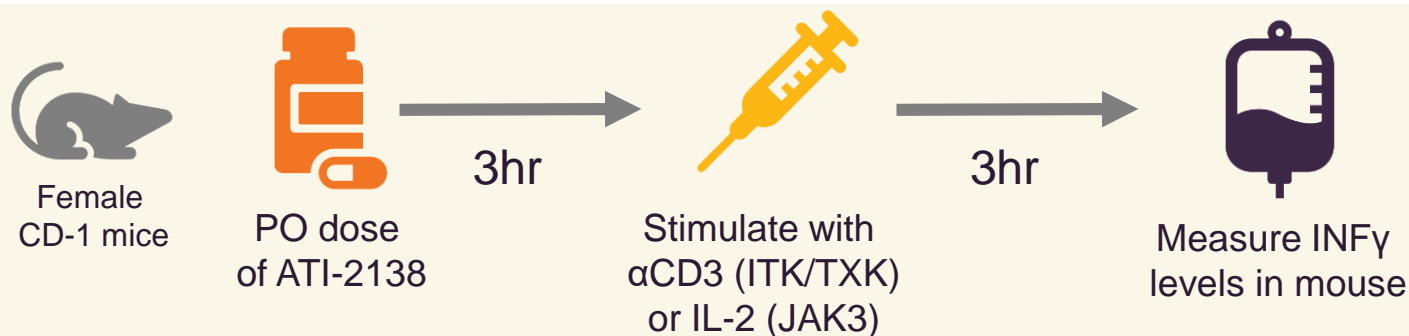


## Pre-clinical Data: ATI-2138 Activity in Cell Based Assays

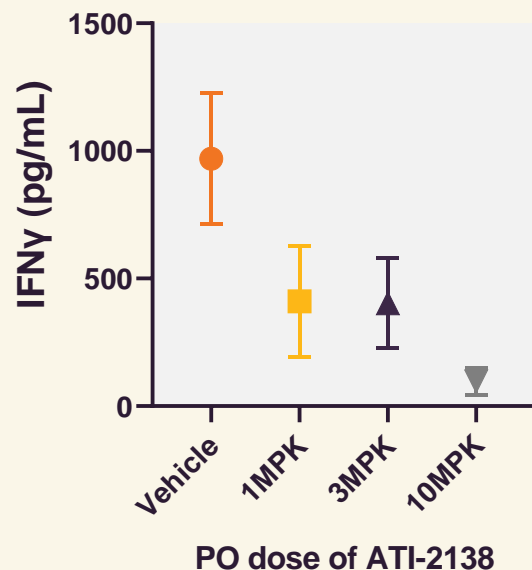
Assay	ATI-2138 ( $\mu$ M)	Assay Description
hJurkat pPLC $\gamma$ -1 IC <sub>50</sub>	0.007	Assesses ITK/TXK activity
hPBMC pSTAT-5 IC <sub>50</sub>	0.02	Assesses JAK1/3 activity
Ramos pPLC $\gamma$ -2 IC <sub>50</sub>	0.052	Assesses BTK activity
HWB $\alpha$ CD3/IL15 IFN $\gamma$ IC <sub>50</sub>	0.013	Assesses both ITK/TXK and JAK3 pathways

ATI-2138 potently inhibits ITK/TXK and JAK3 in cells and in whole blood

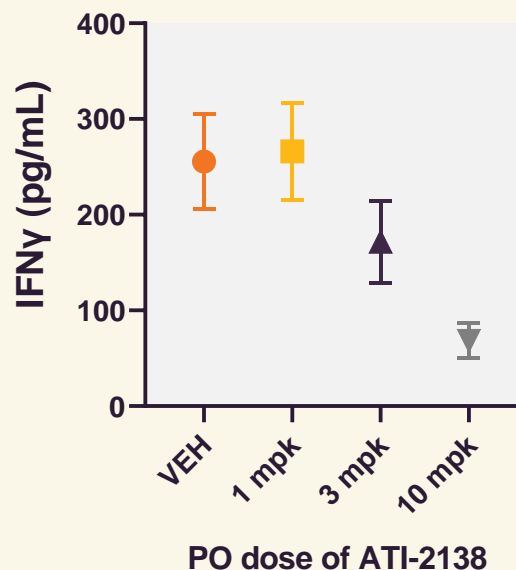
# Mouse Model: ATI-2138 Inhibited ITK/TXK and JAK3 Signaling *In Vivo*



**$\alpha$ CD3 induced IFN $\gamma$  production in mice**

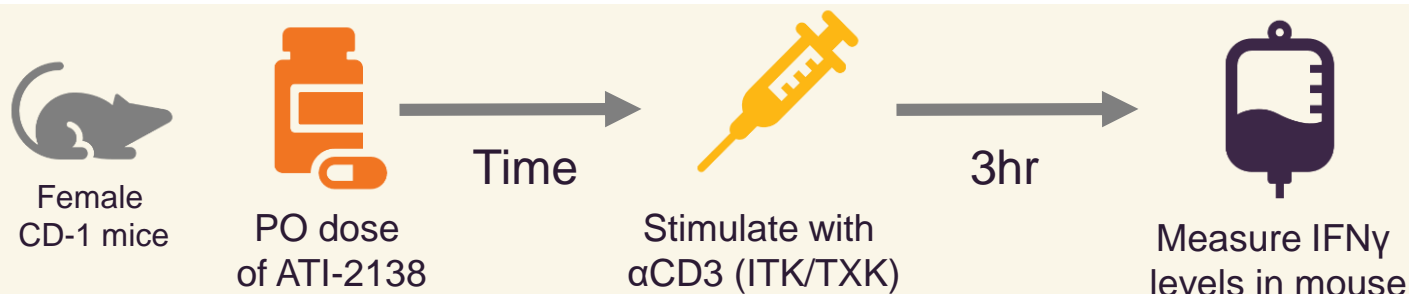


**IL-2 induced IFN $\gamma$  production in mice**

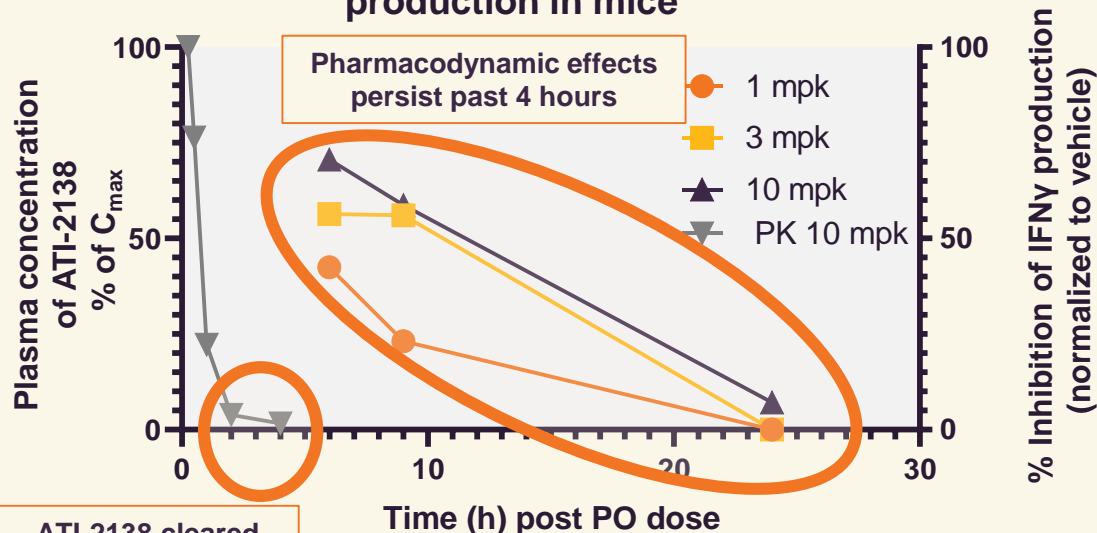


- ATI-2138 potently inhibited TCR signaling *in vivo*
- At higher doses can inhibit both TCR and JAK3 pathways

# Mouse Model: ATI-2138 Had a Prolonged Effect on ITK/TKX Inhibition

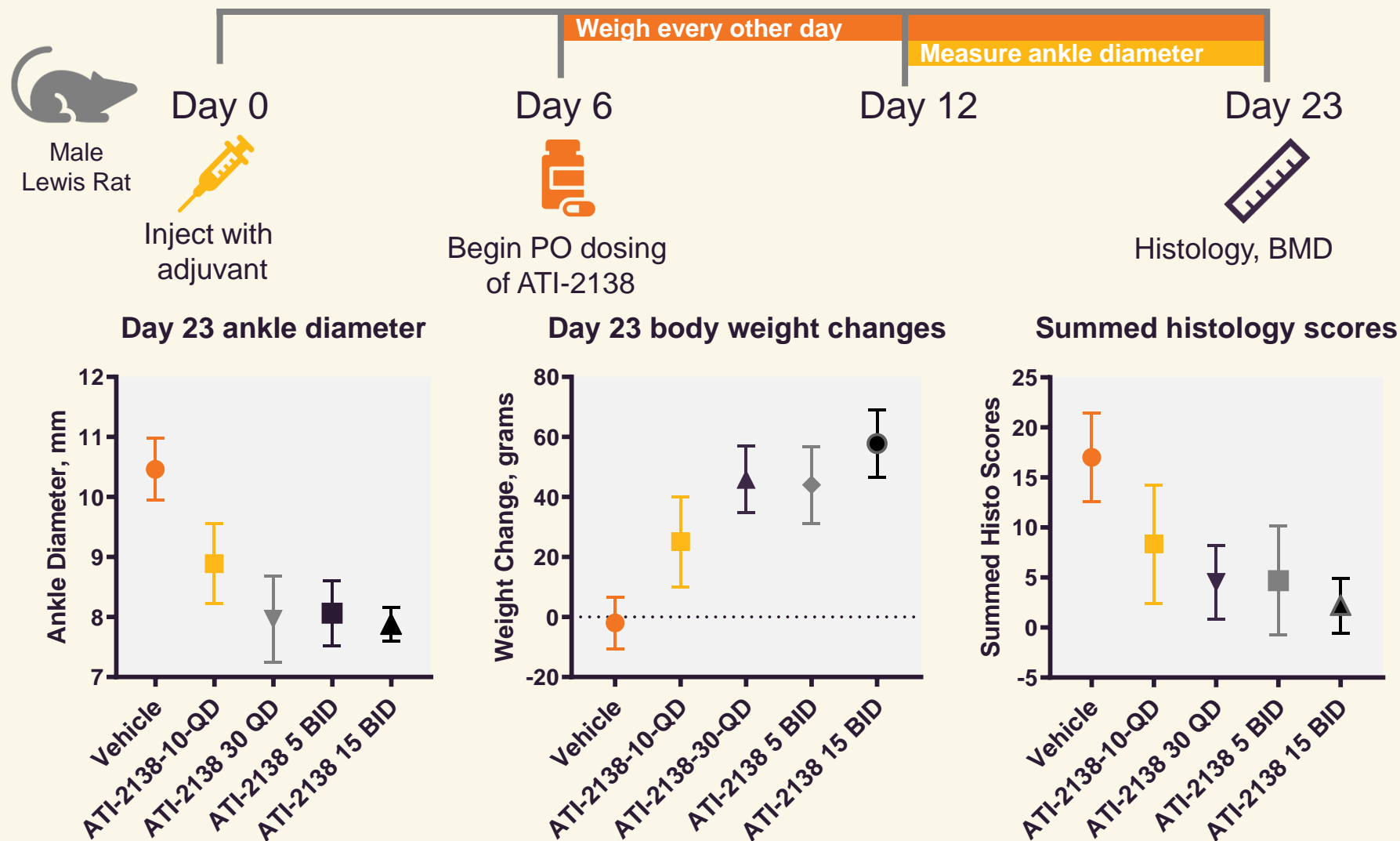


## ATI-2138 PK and $\alpha$ CD3 induced IFN $\gamma$ production in mice



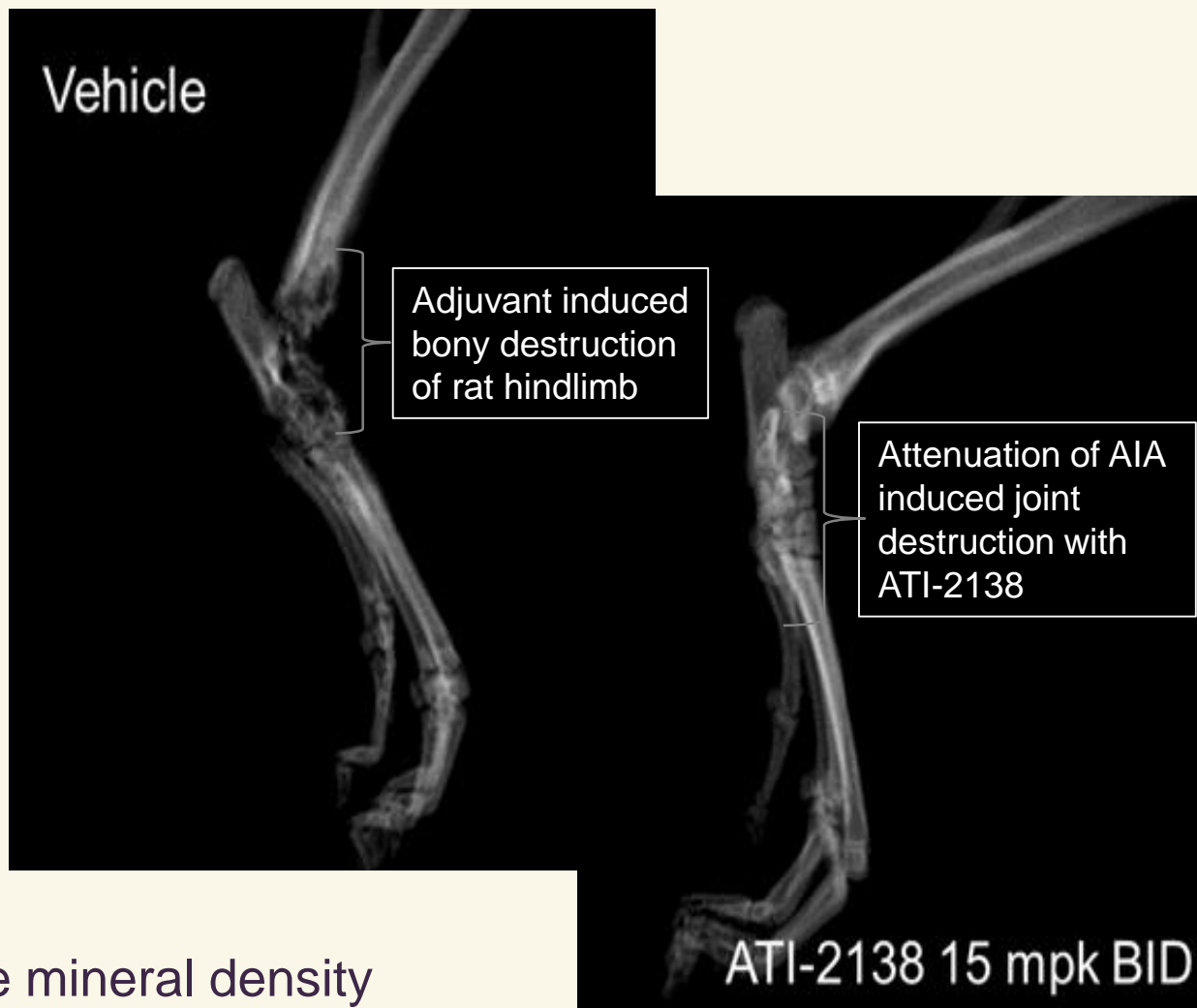
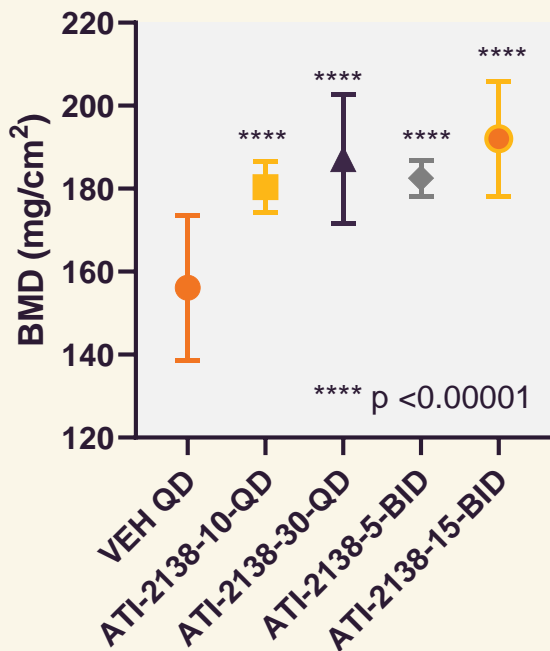
- Due to covalent inhibition of targets, pharmacodynamic effects persisted after compound is cleared from plasma compartment

# Rat Model: ATI-2138 Demonstrated Activity in Rat Adjuvant Induced Arthritis (AIA) model



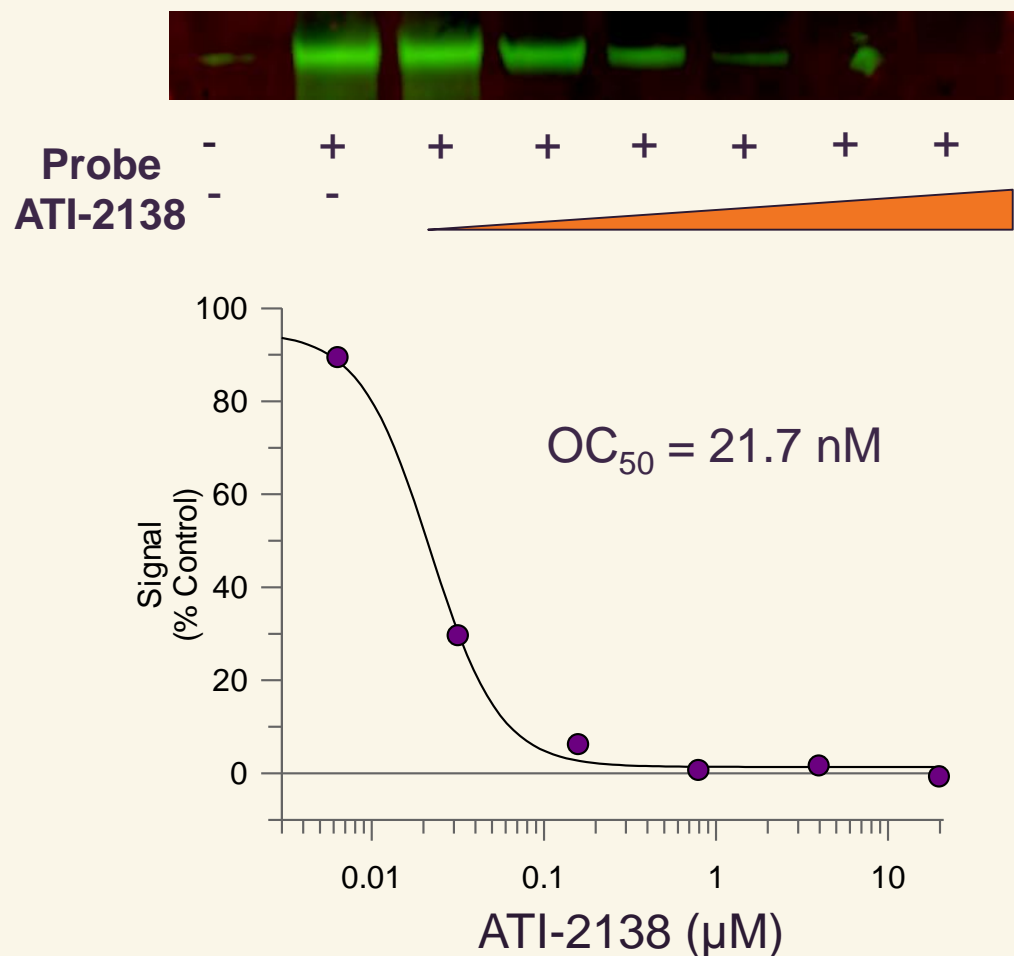
# Rat Model: ATI-2138 Protected Bone in the Rat Adjuvant Induced Arthritis AIA Disease Model

ATI-2138 bone mineral density in rat AIA study



- ATI-2138 reduced bone mineral density loss in rat AIA disease model

# Measuring AT-2138 Occupancy of ITK via Western Blot



- Relationship between PK and PD is complex for covalent inhibitors
  - PD effects continue after compound has been cleared from plasma
  - Recovery rate of target proteins determines duration of effect
- Target occupancy may be assessed *ex vivo* using probe molecules
- $\text{OC}_{50}$  – concentration of an inhibitor at which 50% of its target is occupied

# ATI-2138: Potential Indications

- Moderate-severe psoriasis
- Approved oral therapies
  - OTEZLA (apremilast)
    - Approved in psoriatic arthritis and moderate-to-severe plaque psoriasis in 2014
    - Annual sales of \$472M, \$1.02B, \$1.28B, \$1.61B, from 2015-2018 respectively.<sup>1</sup>
    - Sold to Amgen for \$13.4B
- Probable new entries
  - JAK inhibitors
  - TYK2 inhibitors
- Ulcerative Colitis and/or Crohn's Disease
  - Approved oral therapies
    - Corticosteroids
    - Methotrexate
    - Cyclosporin
    - Tofacitinib
  - Probable new entries
    - Other JAK inhibitors

Good probability of success in psoriasis, IBD, psoriatic arthritis and rheumatoid arthritis with a novel mechanism

Also opportunities for T-cell lymphoma, celiac disease, graft vs host disease, transplant rejection, and asthma



# Current Development Programs - Covalent ITK/TXK/JAK3 Inhibitors

ID	Company	Phase	Indication(s)	Mechanism
PF-06651600	Pfizer	II/III	Alopecia Areata, IBD	JAK3, TEC family
JTE-051	Akros	II	Psoriasis, RA	ITK only
CPI-818	Corvus	I	T cell lymphoma	ITK only
PRN694	Principia	Preclinical	IBD, Psoriasis	ITK/TXK
PF-06465469	Pfizer	Preclinical	N/A	ITK/BTK

- ATI-2138 demonstrated significant potency on ITK/TXK in T-cell based assays<sup>1</sup>
- Little public data about JTE-051, but appears selective for ITK in enzyme and weakly potent in cell assays based on published data<sup>1</sup>
- ATI-2138 has inhibited both ITK and TXK

# ATI-2138: Program Summary and Status

- ATI-2138 is an investigational immunosuppressive compound that targets the TCR and the JAK3 pathways
  - Potent covalent inhibitor of ITK/TKX and JAK3 in enzyme and cell assays
  - *In vitro* and *in vivo* evidence of covalent target modification
  - PD effects persisted after drug is cleared from the plasma compartment
  - ATI-2138 reduces inflammation and preserves bone *in vivo*
  - Biochemical probes available to assess target engagement
- Potential to be useful for a number of autoimmune diseases
- Unique selectivity profile provides opportunity for differentiation from other compounds in clinical development
- Next milestones
  - IND submission in 4Q20/1Q21
  - FIH in 1H 2021

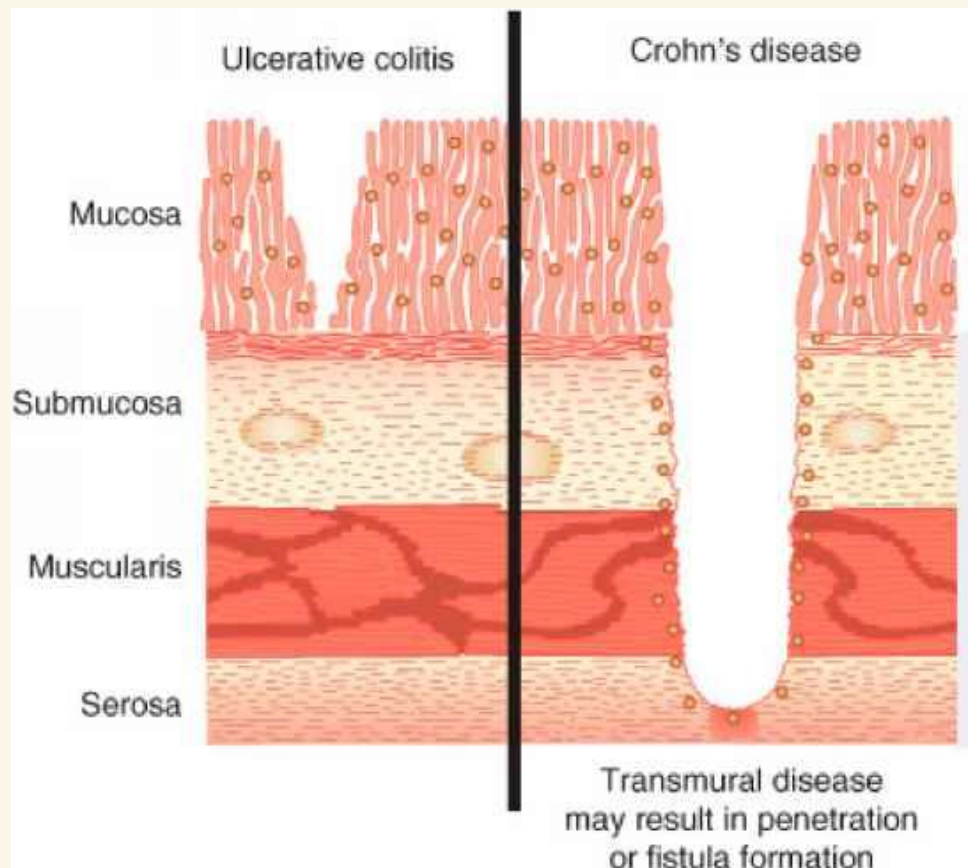
EMPOWERING PATIENTS THROUGH  
**REVELATIONARY**  
SCIENCE

Gut Restricted Inhibitors of  
ITK and/or JAK Kinases  
as Drugs for IBD



# Inflammatory Bowel Diseases (IBD)

- IBD: Ulcerative colitis (UC) and Crohn's disease (CD)
- UC inflammation restricted to inner most layers of the colon (mucosa/submucosa)
- CD inflammation can occur anywhere along digestive tract
- Orally delivered, gut-restricted drugs may be efficacious in UC and CD – ***and potentially result in fewer systemic side effects***



# Advent of JAK Therapy for IBD

## Tofacitinib Approval for UC

- **Ph 3 trial design**
  - 8 wks induction, 10 mg BID
  - If responsive, subjects then randomized to placebo, 5 mg or 10 mg BID
- **1-year remission rates**
  - Placebo – 11%
  - 5mg BID – 34%
  - 10 mg BID – 41%
- **AEs**
  - 5 CV events, 5 skin cancer, increased Herpes zoster
- **Approval**
  - 8 wks 10 mg BID induction, then 5 or 10 mg BID
- **June 2019: Black box** warning added for pulmonary embolism and death risks at 10 mg BID

## Theravance TD-1473

- **Gut restricted** pan-JAK inhibitor
  - kinome selective
- **Preclinical efficacy** (unpublished) at 1 mg/kg BID PO in oxazolone model of murine UC
- **Phase 1b:**
  - 40 patients in UC completed
- **Phase 2b/3:**
  - CD and UC trials ongoing
- **Partnered with Janssen in 2018**
  - ~60 pts of data at time of deal
  - \$100 million upfront
  - \$900 million in additional potential payments

# Gut-Restricted ITK/JAK3 and Reversible JAK Inhibitors

- **Therapeutic Indications:** IBD (UC and CD), Celiac Disease
- **Biological Rationale:**
  - JAK3 required by key cytokines associated with IBD, Celiac Disease
  - ITK dependent T cells drive all autoimmune disease
  - JAK inhibitors clinically active in UC and CD (XELJANZ (tofacitinib) recently approved for UC)
- **Target Candidate Profile:** Potent ITK/TK/JAK3 covalent or JAK1/3 reversible inhibitors that achieve high local concentrations in gut tissue with minimal systemic exposure
- **Potential competitive advantages/multiple shots on goal:**
  - Gut restricted drugs have potential to provide efficacy with reduced safety risks
  - Covalent ITK/JAK3 may offer superior efficacy to JAK3 pathway alone, due to known synergy between the TCR and IL-2 pathway
  - PK advantage with extended PD – efficacy persists until protein turns over
  - Reversible pan JAK inhibitors cover key cytokines (e.g., IL-23, IFN $\gamma$ , etc.)



# Progress to Gut-Restricted IBD Drug

- Identify potent covalent JAK3/ITK and reversible JAK inhibitors
  - Covalent ITK/JAK3 ATX-002 and ATX-001 (investigational compounds) in hand ✓
  - Reversible pan-JAK1 ATX-025 (non-covalent JAK inhibitor) and ATX-023 in hand ✓
  - Initial studies were done with ATX-002 and ATX-025
- Show compounds have minimal systemic/maximum colonic exposure
  - Oral dosing followed by drug level measurements in plasma vs. colon ✓
- Demonstrate activity in short term pharmacodynamic models
  - Inhibition of intrarectal (IR) oxazolone (OXA) challenge-induced cytokine ✓
- Demonstrate activity in short term preclinical activity models
  - Positive results in oxazolone induced colitis short term model ✓
  - 2,4,6-trinitrobenzene sulfonic acid (TNBS) model in development
- Demonstrate activity in long term preclinical disease models
  - Adoptive T cell transfer model with an IL-12/23 antibody as comparator
- Study compounds within initial 4-8 week UC trial



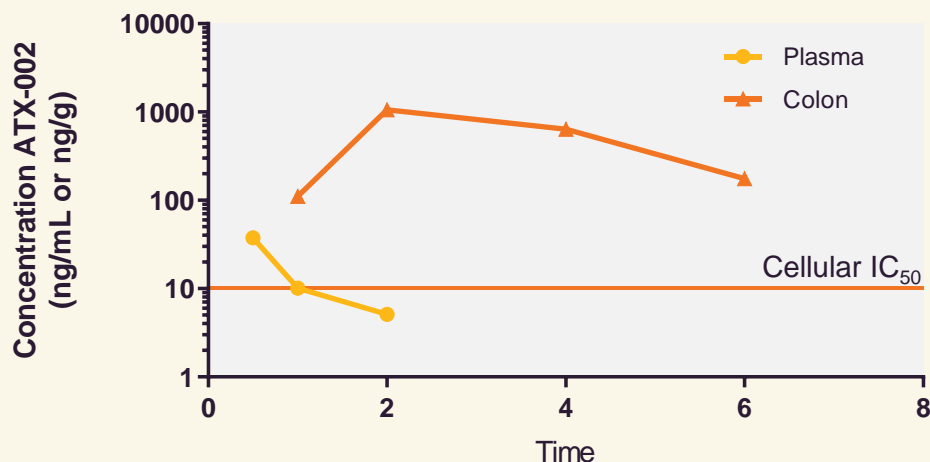
## Preclinical Data: Compound Potencies in Cells

Kinases	ITK/TXK	JAK1/3	JAK1/2	JAK2/2	Tyk2/JAK2
ATX#	Jurkat	IL-2	IFN $\gamma$	GMCSF	IL-12
002	27	42	>4,000	>4,000	>4,000
023	ND	60	270	963	>4000
025	>4,000	50	151	38	61

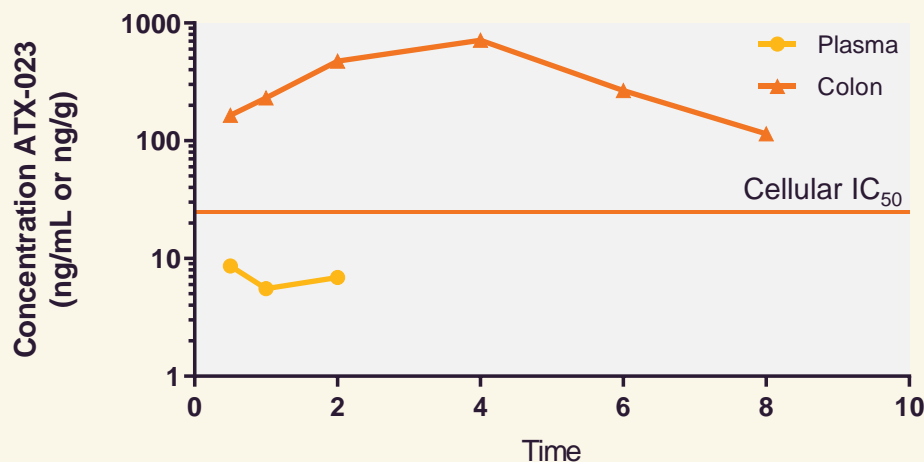
- ATX-002 is covalent inhibitor of ITK, TXK and JAK3, demonstrating potent inhibition of cell activity after T cell receptor and IL-2 receptor signaling, however no inhibition of non-JAK3 cytokine receptors
- ATX-023 is a reversible JAK1/3 inhibitor demonstrating potent inhibition of several key cytokines – likely no effect on T cell receptor
- ATX-025 is a non-covalent JAK inhibitor demonstrating no effect on T cell receptor
- *In vivo* disease model data will ultimately inform which pathways are optimal for treatment in humans

# Mouse Model: Compound Exposure after Oral Dosing

ATX-002 Intestinal vs. Systemic PK  
5 mpk PO in Mice



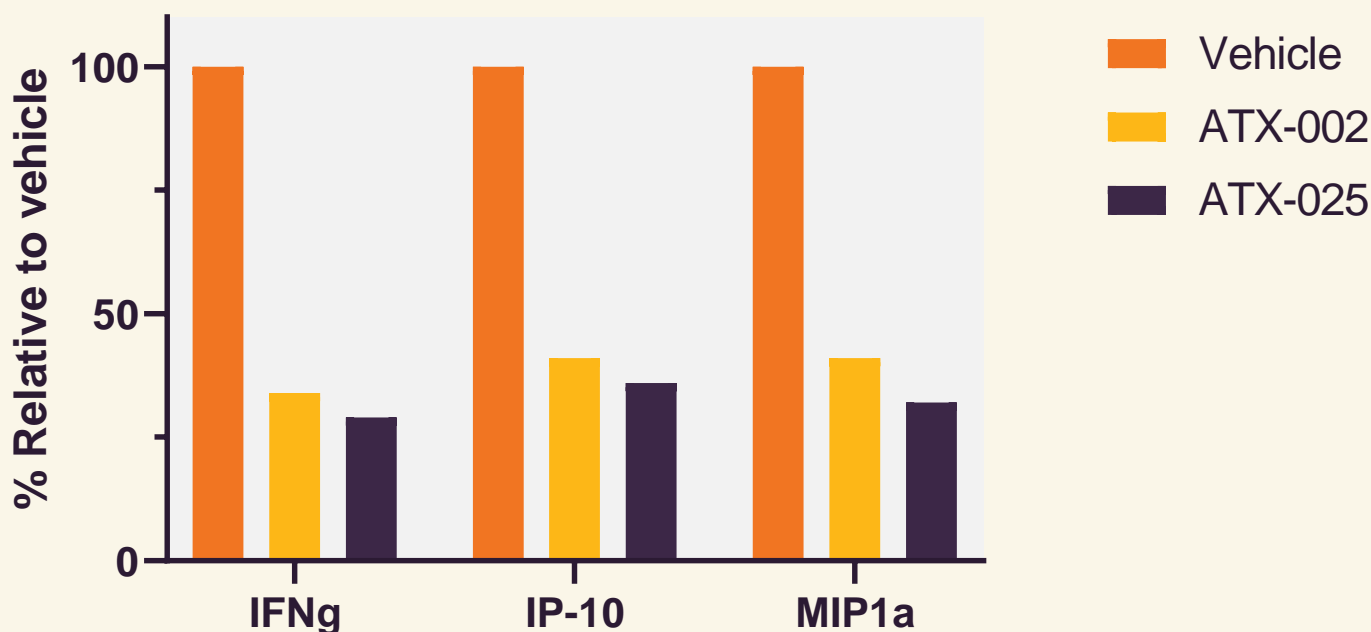
ATX-023 Intestinal vs. Systemic PK  
5 mpk PO in Mice



- ATX-002 (ITK/TXK/JAK3, top)
- ATX-023 (JAK1/3, bottom)
- Significant and sustained exposures in colon after oral dosing
- Minimal drug levels measured in plasma (shown)
  - do not cover cell IC<sub>50</sub> for ATX-023
  - only for initial time point (0.5 h) for ATX-002
  - does not account for protein binding
- PK profile consistent with achieving enhanced colon activity and minimal systemic adverse events

# Mouse Model: ATX-002 and ATX-025 Inhibit OXA Induced Cytokines

## Oxazolone PD Model - Cytokine Inhibition

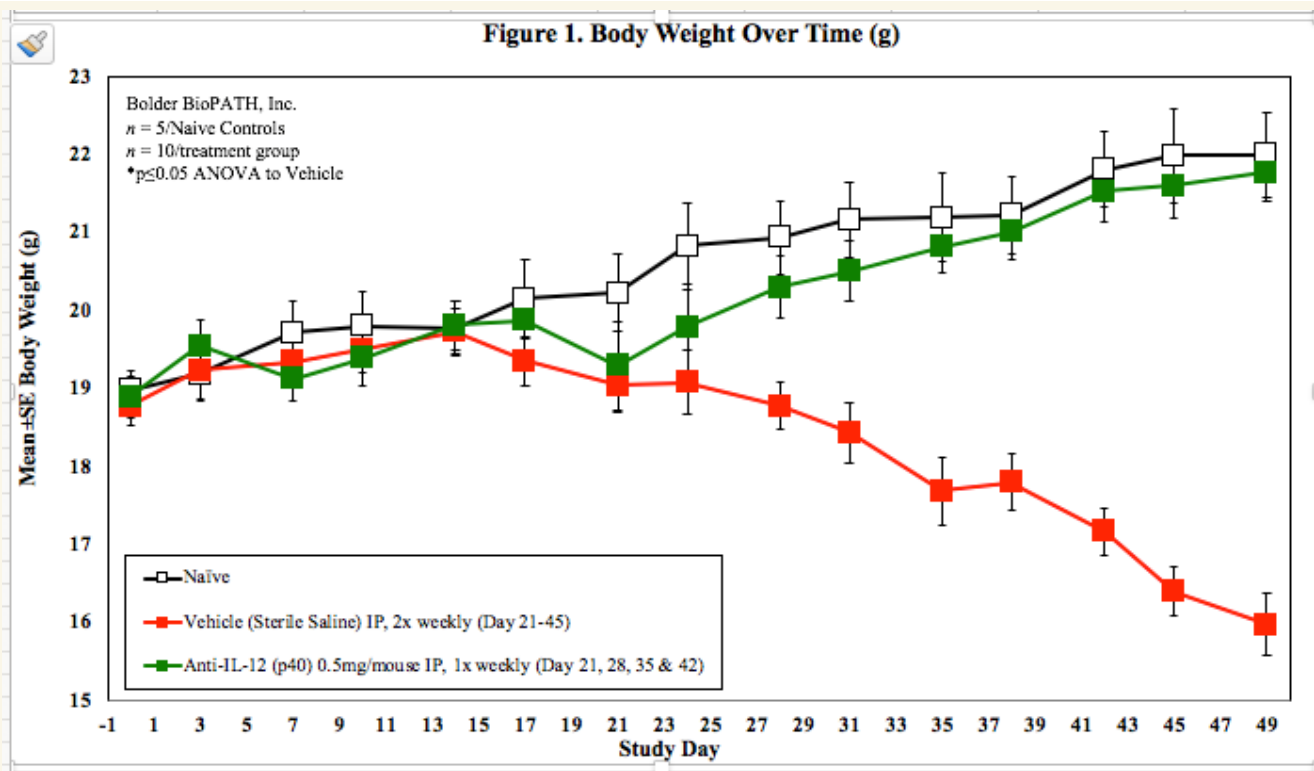


- Shaved mice primed topically with 4% oxazolone. Seven days after priming:
  - 0 hr: Mice dosed PO with ATX-002 or ATX-025, 30 mg/kg
  - 2 hr: Mice injected intrarectally with 100  $\mu$ l, 1% OXA
  - 4 hr: Colons harvested, and lysate analyzed cytokines by ELISA (MSD)
- 3 cytokines significantly inhibited after oral dosing with compound and OXA intrarectal challenge
  - IFN $\gamma$ , IP10 and MIP1 $\alpha$

- [illegible]



# Mouse Model: Bolder Biopath Adoptive Transfer T Cell Colitis Model



- Adoptive transfer of naïve T cells into SCID mice results in colitis
- In-life readout is weight loss over 48 days (shown)
- Colon weight/length and terminal histology at end
- Translatable model as antibody to IL-12/23 (surrogate for Stelara) is active when dosed therapeutically (green line)
- ATX-025 (non-covalent JAK inhibitor) currently in study

# Gut Restricted Drug Development - Summary

- Potent compounds found in both series:
  - ITK/TXK/JAK3 covalent and JAK1/3 non-covalent
- Compounds have gut-restricted PK post oral dosing
- Compounds active in short-term PD and efficacy models (OXA), with alternative models in development (e.g., TNBS-induced colitis)
- Lead compounds being studied in T cell adoptive transfer model with clinically validated comparator ( $\alpha$ IL-12/23)
- Expect to identify a reversible JAK candidate 4Q19.
- Lead optimization targeting ITK/TXK/JAK3 with covalent candidate selection in 2020

# Catalysts

Milestone	2019		2020			
	Q3	Q4	Q1	Q2	Q3	Q4
A-101 45% Common Warts						
Phase 3 Data (Thwart-1, Thwart-2)	✓					
Inflammation / Immunology						
ATI-450 (MK2 Inhibitor) - Initiate Phase 1 Trial (SAD/MAD)	✓					
ATI-450 (MK2 Inhibitor) - Phase 1 Data (SAD/MAD)						
ATI-450 (MK2 Inhibitor) - Initiate Phase 2 Trial in Rheumatoid Arthritis						
ATI-450 (MK2 Inhibitor) - Phase 2 data in RA						
ATI-1777 (Soft JAK) – Submit IND						
ATI-1777 (Soft JAK) – Initiate Phase 1 Trial						
ATI-2138 (ITK/JAK3) – Submit IND						



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**THANK YOU**

