UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

FORM 8-K

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

Date of Report (Date of earliest event reported): September 27, 2019

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

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

640 Lee Road, Suite 200
Wayne, PA 19087
(Address of principal executive offices, including zip code)

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

N/A
(Former name or former address, if changed since last report)

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

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

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

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

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

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

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

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

Emerging growth company ☑

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

Item 7.01 Regulation FD Disclosure.

On September 27, 2019, Aclaris Therapeutics, Inc. (the "***Company***") will host an R&D day in New York, New York, and a live webcast of the event will be available through the Events page of the Investors section of the Company's website. The R&D day will include a slide presentation. A copy of this slide presentation is furnished as Exhibit 99.1 to this Current Report on Form 8-K.

In accordance with General Instruction B.2. of Form 8-K, the information in this Item 7.01 and Exhibit 99.1 hereto shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "***Exchange Act***"), or otherwise subject to the liability of that section, nor shall it be deemed incorporated by reference in any of the Company's filings under the Securities Act of 1933, as amended, or the Exchange Act, whether made before or after the date hereof, regardless of any incorporation language in such a filing, except as expressly set forth by specific reference in such a filing.

Item 9.01 Financial Statements and Exhibits.

Exhibit No.	Exhibit Description
99.1	Company Presentation.

SIGNATURES

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

ACLARIS THERAPEUTICS, INC.

By: /s/ Frank Ruffo
Frank Ruffo
Chief Financial Officer

Date: September 27, 2019

EMPOWERING PATIENTS THROUGH
REVELATIONARY
SCIENCE

Aclaris Therapeutics Research & Development Day

September 27, 2019

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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 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[1]
    - 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.

1 Factset Drug sales data

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)
2018E WW Sales[1]	~25B	~15B	~$5B	~$11B	~$1B
Estimated Peak Market (WW)[2]	~$25-30B	~$20-25B	~$8-12B	~$15B	~$8-12B
Prevalent US Moderate/Severe Population[3]	~1,000K+	~1,000-1,300K	~400-500K	~350-450K	~300-700K
Approved Agents (per target)	TNF-alpha: 5	TNF-alpha: 3	TNF-alpha: 2	TNF-alpha: 3	IgE: 1
	CD20: 1	IL-12 / IL-23: 2	Integrin α4β7: 1	IL-12 / IL-23: 1	IL-5: 3
	JAK: 2	IL-17A: 2	JAK: 1	Integrin α4β7: 1	IL-4R: 1
	Integrin α4β7: 1	PDE4: 1			
	Other: 3				
Agents in Clinic (per target)	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 α4β7: 1	IL-4R: 1
	T-cell Receptor: 1		Others: 12	Others: 12	IL-5: 1
	Others: 41				Others: 6
Opportunity for New Treatments	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 biologics/novel agents in the US: R 350-400k / Psoriasis300-350k / Ulcerative Colitis 225-275k / Atopic Dermatitis 150-200k / Asthma 275-325k

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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[1]
  - Worldwide cumulative prevalence of 15-20%[1]
  - 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)[2]
  - Projected to be ~$4.5 billion in 2024[3]
- 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

1 James W, et al Andrew's Diseases of the Skin Clinical Dermatology, 2011, 11th edition
2 Auster M., et al. Something Big Is Getting Bigger [research note]. New York, NY: Credit Suisse Equity Research; 2019.
3 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[1]
  - In the US the number of patients with autoimmune diseases being treated per year is up 63% since 2013[2]
  - 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[3]
  - 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

1 IQVIA - the-global-use-of-medicine-in-2019-and-outlook-to-2023 – pg48
2 5-19 - IQVIA -Medicine Use and pending in the U.S. A Review of 2018 and Outlook to 2023 - pg13
3 Factset Drug sales data

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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 the 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[1]
  - Oral therapy
- ITK/JAK3:
  - Psoriasis market of $15 billion in 2018[1]
  - Oral therapy

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

Inflammation Market Opportunity

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

- Market opportunity[1]:
  - 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.[2]
- 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.[3]
- Market need for Gut restricted options:
  - Targeted therapy with favorable risk/benefit profile

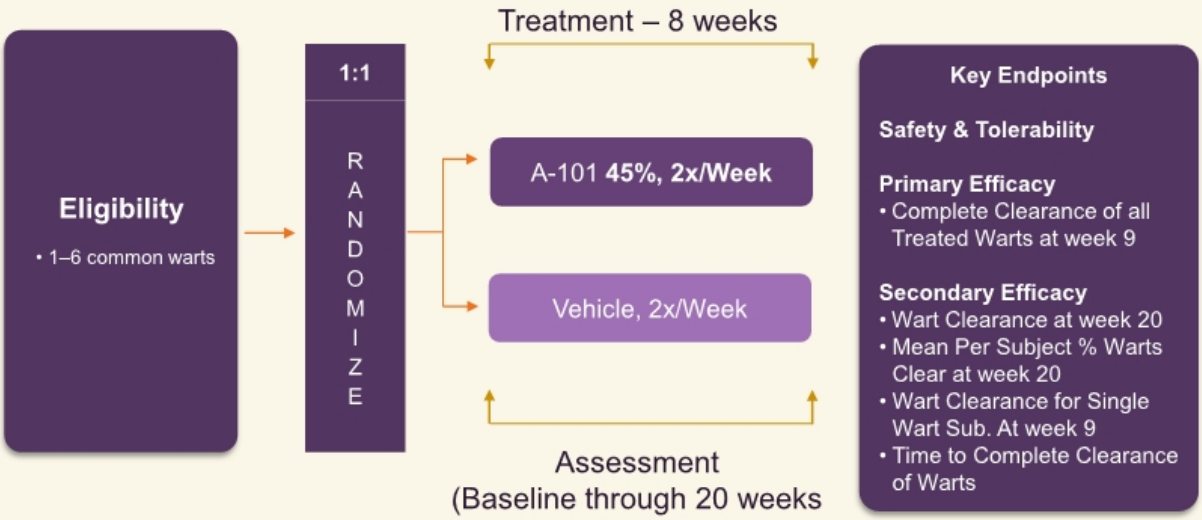
1 Therapeutic Categories Outlook - Cowen and Company, March 2019
2 Patel, Haridarshan, Trevor Lissoos, and David T. Rubin. PloS one (2017)
3 Null, Kyle D., et al. Value in Health (2017) -Ulcerative Colitis Treatment Patterns and Cost of Care

Pipeline: New Focus

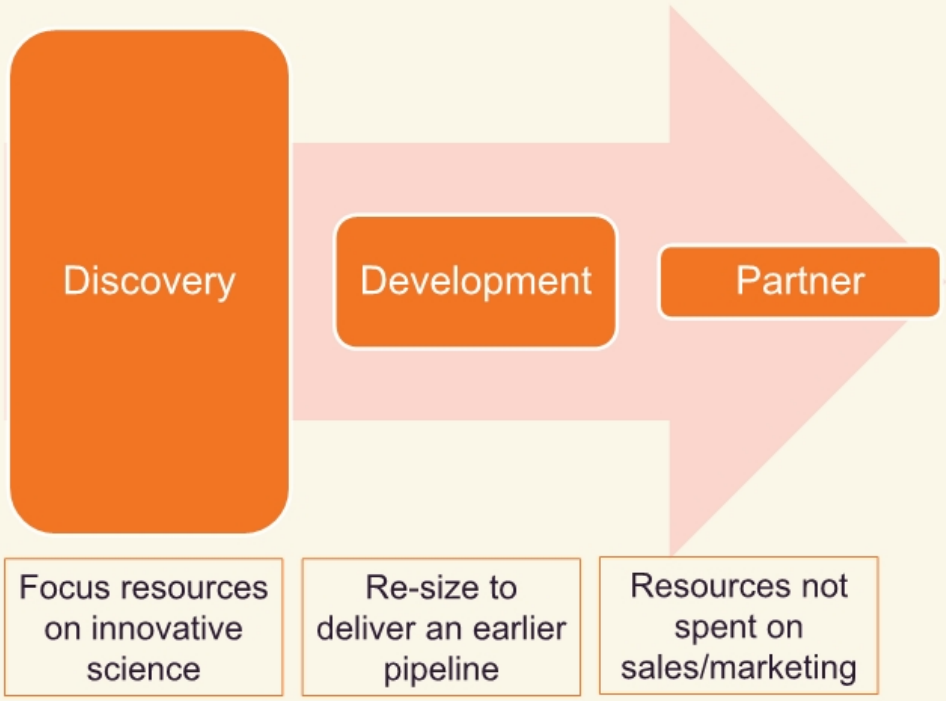
Program	Indication(s)	Preclinical	Phase 1	Phase 2	Phase 3
A-101(45%) *Topical*	Common Warts				
ATI-450 MK2 Pathway Inhibitor *Oral*	RA, Psoriasis				
ATI-1777 JAK1/JAK3 Inhibitor *Soft Topical*	Atopic dermatitis				
ATI-2138 ITK/TXK/JAK3 Inhibitor *Oral*	Psoriasis, Inflammatory Dermatoses				
ITK/JAK3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



Focus resources on innovative science	Re-size to deliver an earlier pipeline	Resources not spent on sales/marketing

Discovery Leaders

Walter Smith *SVP, R&D*	**Joseph Monahan, PhD** *Exec. VP R&D (Head of Discovery)*	**Jon Jacobsen, PhD** *VP, Chemistry*
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	Former Executive Director, Pfizer Inflammation Research and Leader of Global Kinase Technology Team >95 publications and patents (>30 total on kinases)	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*	**David R Anderson, PhD** *Sr. Director, Discovery and Early Development*	**Gary DeCrescenzo** *SVP, Pharm Dev*
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®	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	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	

EMPOWERING PATIENTS THROUGH
REVELATIONARY
SCIENCE

The KINect™ Platform: Our Drug Discovery Engine

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THERAPEUTICS

Technology Platform

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The Kinase Opportunity and Challenge

Creating New Medicines Targeting Previously Inaccessible Kinome Targets

Medically Important and Productive Target Class

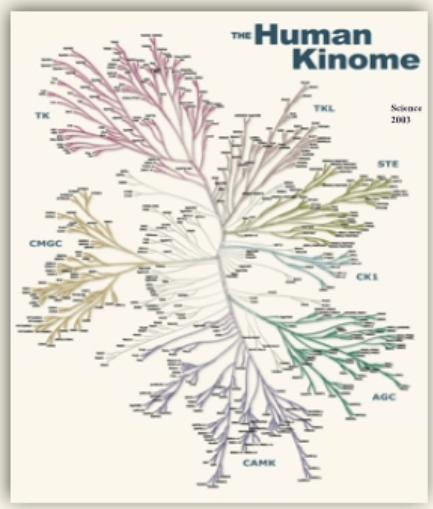
OFEV (nintedanib) capsules 150mg
Bosulif bosutinib
IBRANCE palbociclib
IRESSA
Inlyta axitinib
imbruvica (ibrutinib)
ZELBORAF (vemurafenib) tablets
ICLUSIG (ponatinib) tablets
COMETRIQ (cabozantinib)
gleevec (imatinib mesylate) tablets
GILOTRIF (afatinib) tablets
Tarceva erlotinib
ICLUSIG (ponatinib) tablets
Votrient pazopanib tablets 200 mg
Tykerb (lapatinib)
Jakafi ruxolitinib
SPRYCEL dasatinib
Zydelig (idelalisib) tablets
Caprelsa (vandetanib) tablets
Mekinist (trametinib)
XALKORI crizotinib
Stivarga (regorafenib)
SUTENT sunitinib malate
ZYKADIA ceritinib
Nexavar (sorafenib) tablets
LENVIMA (lenvatinib) capsules
Tasigna nilotinib
XELJANZ (tofacitinib citrate)

~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

*Unexplored opportunities in the druggable human genome Nature Review Medicine

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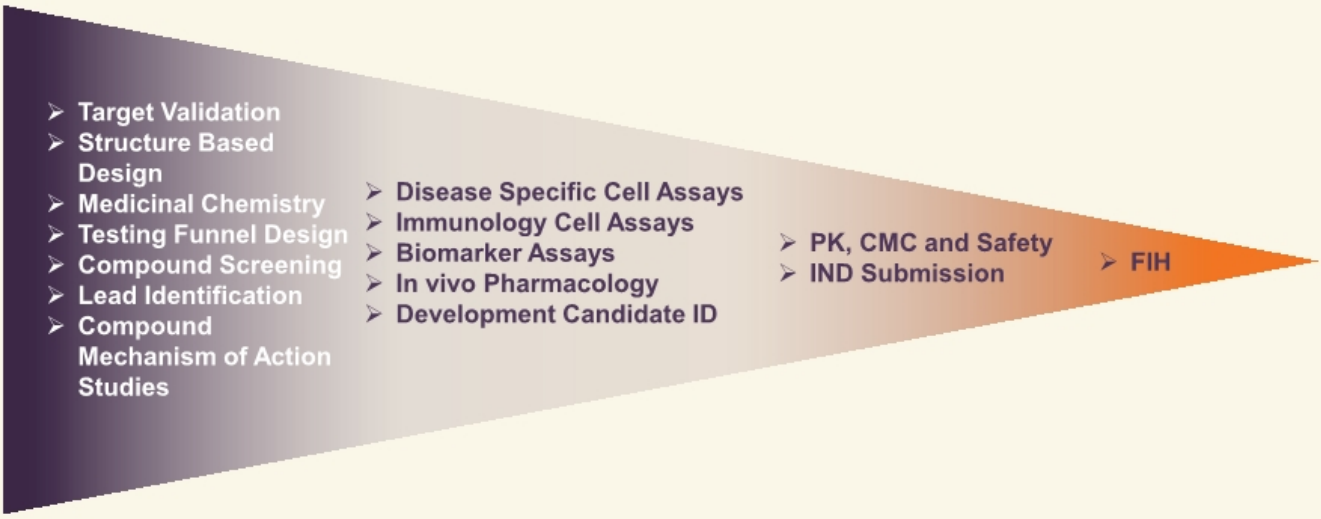
The Aclaris Solution: The KINect™ Technology Platform

- 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



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**

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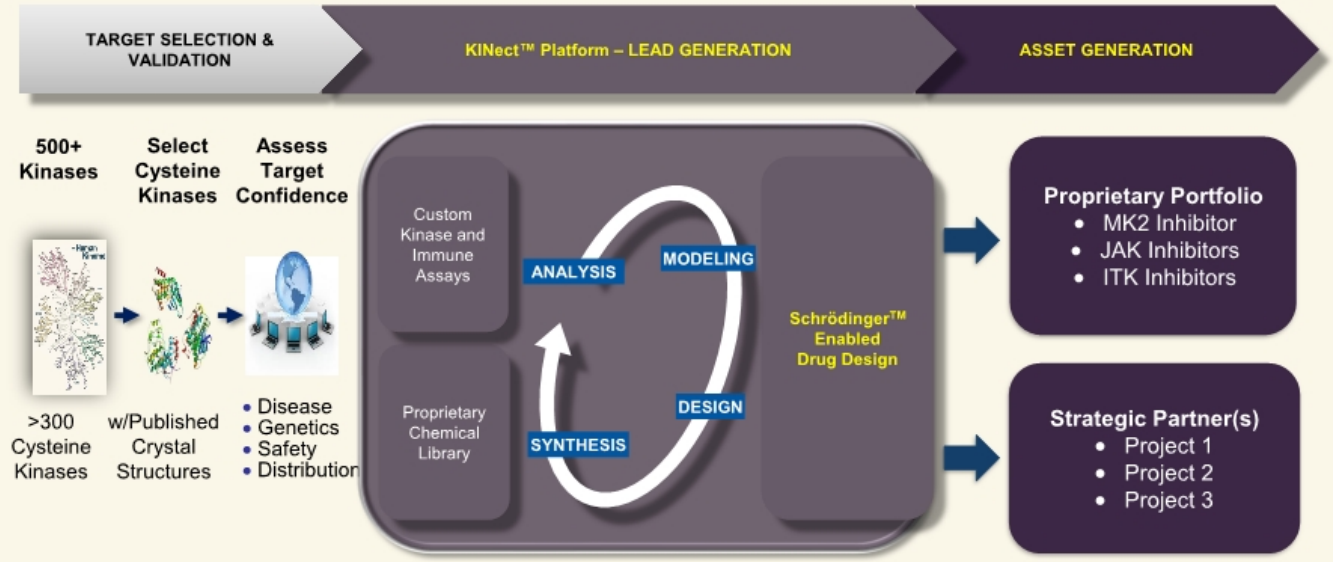
KINect™ Platform
Developing Kinase Drug Candidates Rapidly & Efficiently



- **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**

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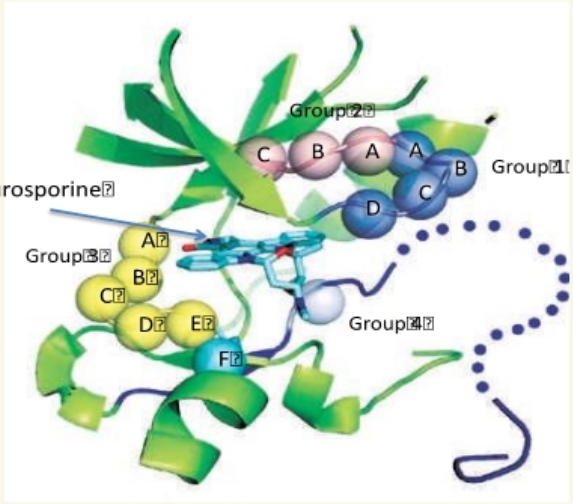
KINect™ Platform Demonstrated Success
Reversible and Covalent

MK2 Pathway Inhibitor	Tissue Restricted JAK Inhibitors	Covalent ITK Inhibitors
Unique Substrate Selective Drug Design	**Tailoring physico-chemical and potency properties**	**Covalent Inhibition: Solution for difficult to target kinase**
• 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	• 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	• 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)*

- 313 of the 518 human protein kinases contain a cysteine near the active site
- Covalent drugs target these cysteine residues

- 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**

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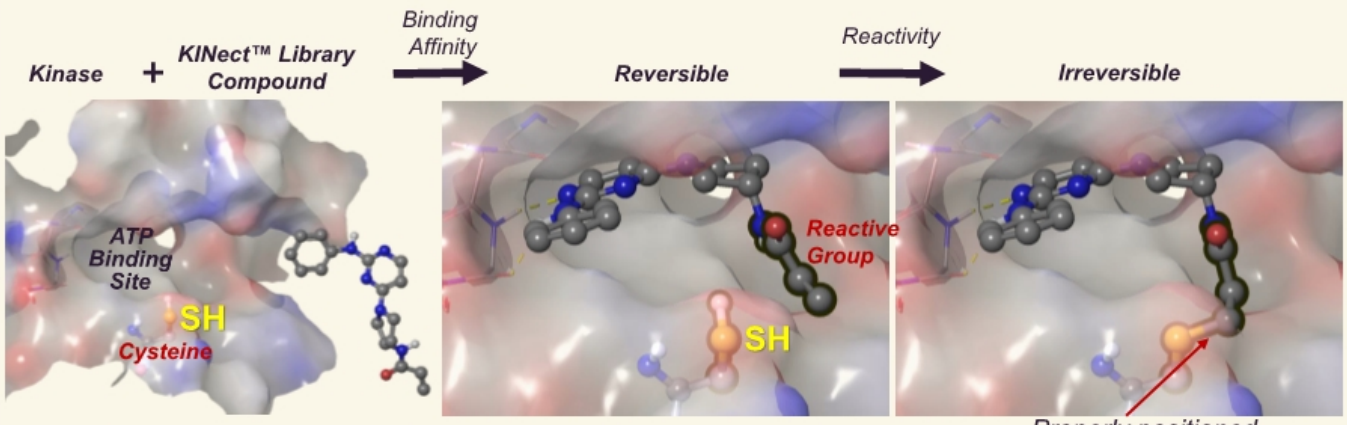
KINect™ Technology Platform
Discovery of covalent kinase inhibitors



Precise placement of reactive group provides enormous rate enhancement for covalent bond formation

Properly positioned reactive group covalently binds cysteine on kinase

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

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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

cysteinome	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
CDD-000295	44.0	57.0	28.0	1.0	24.0	21.0	46.0	-3.0
CDD-000296	-4.0	7.0	-8.0	12.0		12.0	-6.0	13.0
CDD-000297	61.0	68.0	-5.0	31.0	99.0	78.0	0.0	5.0
CDD-000298	27.0	17.0	-7.0	33.0	55.0	35.0	41.0	5.0
CDD-000299	-1.0	-7.0	-14.0	-12.0		10.0	-4.0	15.0
CDD-000300	16.0	35.0	-7.0	-33.0	12.0	12.0	0.0	28.0
CDD-000301	21.0	7.0	1.0	-36.0	17.0	28.0	38.0	2.0
CDD-000302	12.0	10.0	1.0	-13.0	14.0	7.0	9.0	18.0
CDD-000303	68.0	94.0	53.0	9.0	13.0	9.0	80.0	35.0
CDD-000304	6.0	1.0	9.0	34.0	17.0	19.0	34.0	16.0
CDD-000305	4.0	-6.0	-1.0		10.0	15.0	8.0	21.0
CDD-000306	82.0	28.0	67.0	94.0	26.0	-16.0	81.0	3.0
CDD-000307	93.0	97.0	135	84.0	100	99.0	101	174
CDD-000308	5.0	17.0	-9.0	-21.0	31.0	-1.0	-1.0	10.0
CDD-000309	7.0	18.0	-10.0	-45.0	9.0	10.0	3.0	-4.0
CDD-000310	5.0	15.0	-8.0	45.0	49.0	9.0	66.0	14.0
CDD-000311	91.0	90.0	73.0	98.0	85.0	95.0	83.0	56.0
CDD-000312	74.0	94.0	80.0	61.0	24.0	5.0	43.0	3.0
CDD-000313	8.0	81.0	-8.0	46.0	4.0	22.0	-3.0	-3.0
CDD-000314	-83.0		-428	-55.0	15.0	8.0	-23.0	-65.0
CDD-000315	-37.0	28.0	-26.0	24.0	7.0	5.0	20.0	2.0
CDD-000316	23.0	16.0	-19.0	-28.0	77.0	43.0	5.0	10.0
CDD-000317	8.0	-9.0	-22.0	-83.0	25.0	19.0	13.0	-7.0
CDD-000318	3.0	14.0	-26.0	-39.0	10.0	10.0	8.0	1.0
CDD-000319	5.0	-7.0	-11.0	8.0	15.0	3.0	-5.0	23.0
CDD-000320	2.0	12.0	-12.0	13.0	5.0	15.0	-5.0	19.0
CDD-000321	1.0	-9.0	0.0	28.0	15.0	4.0	-1.0	9.0
CDD-000322	-1.0	-4.0	-295	-4.0	14.0	10.0	11.0	18.0
CDD-000323	4.0	-6.0	-4.0	-16.0	8.0	4.0	-4.0	34.0
CDD-000324	10.0	-8.0	-3.0	29.0	68.0	19.0	0.0	30.0
CDD-000325	11.0	-2.0	-3.0	-59.0	12.0	27.0	1.0	31.0
CDD-000326	16.0	16.0	-6.0	-31.0	16.0	12.0	-9.0	24.0
CDD-000327	-2.0	-6.0	-7.0	7.0	2.0	23.0	4.0	0.0
CDD-000328	-7.0	-6.0	-1.0	14.0	14.0	10.0	-1.0	0.0
CDD-000329	0.0	-8.0	-14.0	18.0	10.0	16.0	0.0	14.0

cysteinome	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
CDD-000330	2.0	-13.0	-6.0	-6.0	12.0	53.0	5.0	17.0
CDD-000331	-11.0	3.0	-7.0	-39.0	23.0	9.0	11.0	-2.0
CDD-000332	-2.0	-1.0	-12.0	-37.0	15.0	17.0	10.0	16.0
CDD-000333	-3.0	-6.0	-4.0	-90.0	6.0	15.0	13.0	-8.0
CDD-000334	-3.0	-10.0	-10.0	-50.0	9.0	3.0	9.0	2.0
CDD-000335	-7.0	5.0	-6.0	17.0	24.0	24.0	1.0	2.0
CDD-000336	-2.0	-27.0	-3.0	18.0	-24.0	15.0	1.0	7.0
CDD-000337	0.0	3.0	4.0	21.0	18.0	15.0	-6.0	15.0
CDD-000338	13.0	-7.0	4.0	4.0	22.0	3.0	-5.0	7.0
CDD-000341	19.0	25.0	5.0	56.0	26.0	80.0	0.0	19.0
CDD-000342	5.0	-9.0	-7.0	-14.0	14.0	17.0	-1.0	14.0
CDD-000343	22.0	21.0	19.0	-32.0	26.0	48.0	66.0	8.0
CDD-000344	13.0	3.0	6.0	5.0	26.0		21.0	43.0
CDD-000345	-20.0	7.0	-7.0	60.0	34.0	84.0	12.0	3.0
CDD-000346	26.0	18.0	23.0	68.0	56.0	61.0	78.0	20.0
CDD-000347	23.0	5.0	16.0	67.0	20.0	29.0	36.0	51.0
CDD-000348	63.2	36.5	35.6	45.0	37.0	25.9	70.7	
CDD-000350	2.0	3.0	-2.0	-34.0	13.0	10.0	5.0	12.0
CDD-000361	17.0	19.0	0.0	27.0	47.0	64.0	26.0	18.0
CDD-000362	21.0	27.0	-6.0	32.0	12.0	59.0	9.0	14.0
CDD-000363	7.0	13.0	0.0	57.0	17.0	28.0	20.0	36.0
CDD-000364	7.0	-1.0	5.0	33.0	4.0	12.0	7.0	19.0
CDD-000415	57.0	88.0	-11.0	21.0	39.0	21.0	2.0	5.0
CDD-000416	-27.0	13.0	9.0	28.0	35.0	1.0	3.0	5.0
CDD-000417	-3.0	15.0	14.0	36.0	15.0	5.0	-2.0	2.0
CDD-000432	54.0	10.0	34.0	49.0	14.0	3.0	30.0	15.0
CDD-000433	52.0	-17.0		74.0	16.0	4.0	53.0	-43.0
CDD-000434	81.0	20.0	65.0	30.0	35.0	17.0	64.0	50.0
CDD-000435		15.0	53.0	-9.0	22.0	14.0		43.0
CDD-000436	92.0	-3.0	81.0	70.0	-1.0	8.0	86.0	52.0
CDD-000437	69.0	53.0	69.0	68.0	32.0	-25.0	83.0	32.0
CDD-000438	24.0	6.0	50.0	51.0	-3.0	10.0		7.0
CDD-000439	81.0	67.0	90.0	30.0	0.0	2.0	2.0	18.0
CDD-000440	96.0	96.0	107	69.0	8.0	9.0	42.0	20.0

*Circled compounds indicate starting points for specific kinases

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

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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	**Yes**	**No**	**No**
Multiple scaffolds/templates	**8-10**	**Patents limited to 1-2**	**Patent limited to 1**
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)

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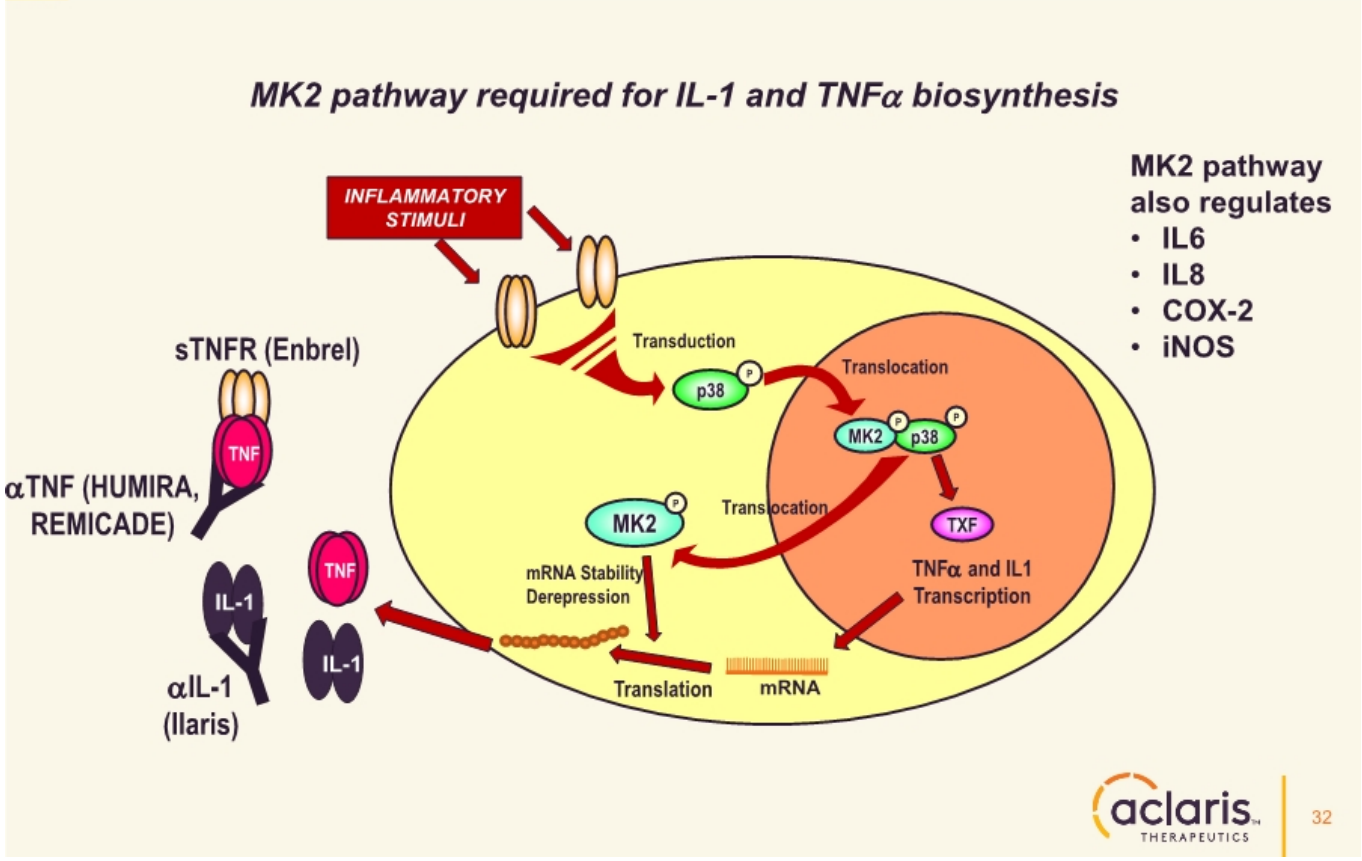
MK2 Inhibitor – Potential ORAL Alternative to Injectable, Anti-Cytokine Biologics and JAK Inhibitors for Immuno-Inflammatory Diseases

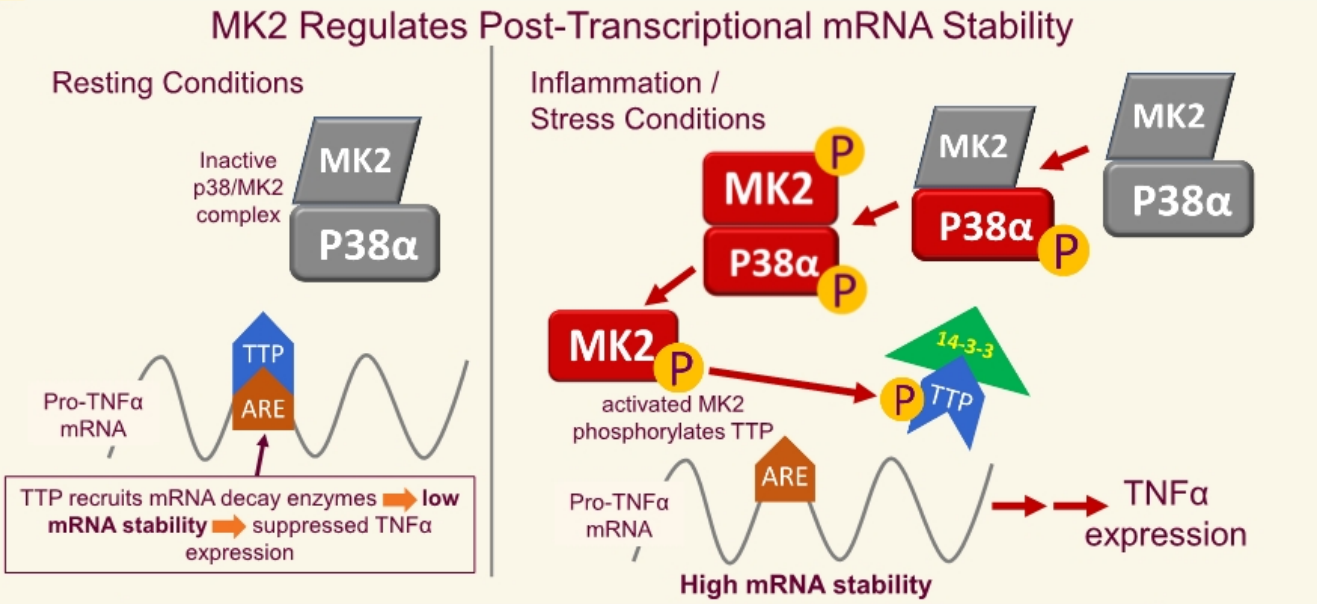
- MK2* is an attractive drug target because it drives pro-inflammatory cytokine expression associated with the p38 MAP kinase pathway
- The effects of inhibiting MK2 mirror the effects of anti-inflammatory biologics[1]
  - **anti-TNF**: HUMIRA®, ENBREL®, REMICADE®
  - **anti-IL1**: KINERET®, ILARIS®, ARCALYST®
  - **anti-IL6**: KEVZARA®, ACTEMRA®
- 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

*MK2 = Mitogen-activated protein kinase-activated protein kinase 2
1 Data on file

Intracellular Pathways Regulate Cytokine Production



MK2 Post-Transcriptionally Regulates TNFα and Other Key Pro-Inflammatory Cytokines



- 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 | P Phosphate group

*Data on file

Historical Development of p38 Inhibitors:
Off-target tox, on-target tox, tachyphylaxis

- 1st generation failed due to safety profile
  - Off-target effects – poor kinase selectivity
  - On-target tox liabilities
- 2nd 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-α and –γ 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

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p38 MAPK Substrates

Transcription Factor	DNA Binding	Regulatory Protein	RNA Binding
Atf2	BAF60c	BimEL-BCL2L11	FBP2/3
C/EBPβ	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	GSK3β	p47phox-NCF1	**Endosome**
MRF4-MYF6	MK2-MAPKAPK2	p57kip2-CDKN1C	EEA1
p53-TP53	MK3-MAPKAPK3	PIP4Kβ-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	PKCε		Lamin B1

Trempolec et al. 2013. Snapshot: p38 MAPK Substrates. CELL

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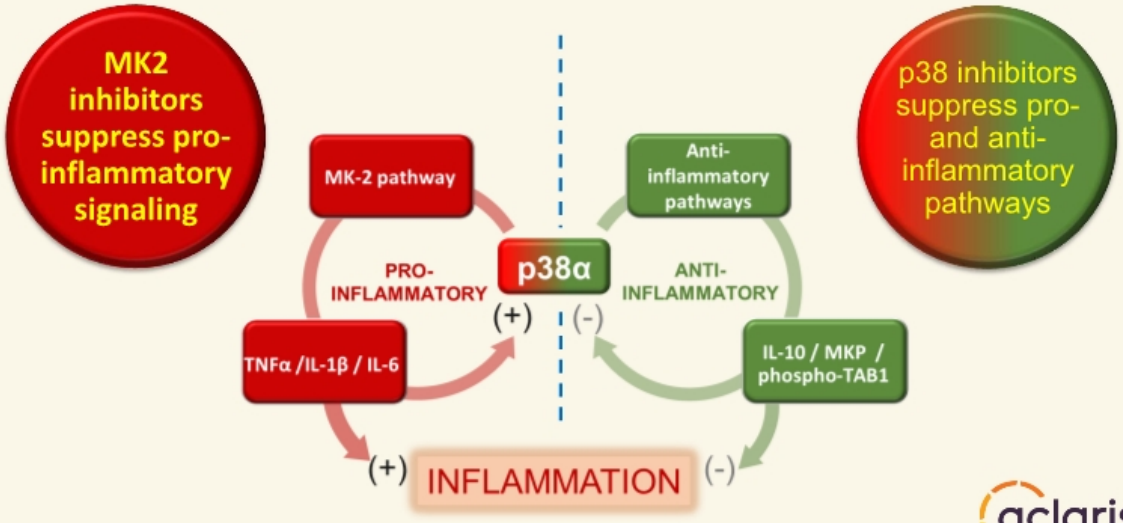
The Path From p38 to MK2

- p38 was the original therapeutic target for suppressing TNFα 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.



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

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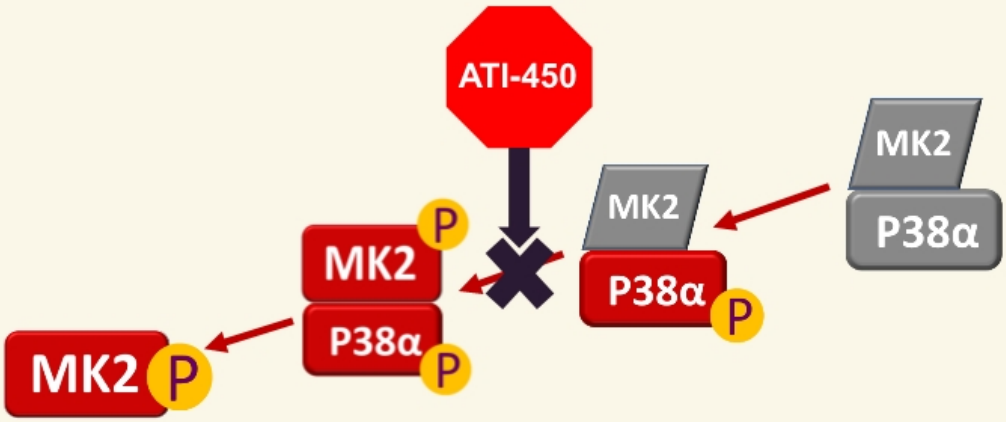
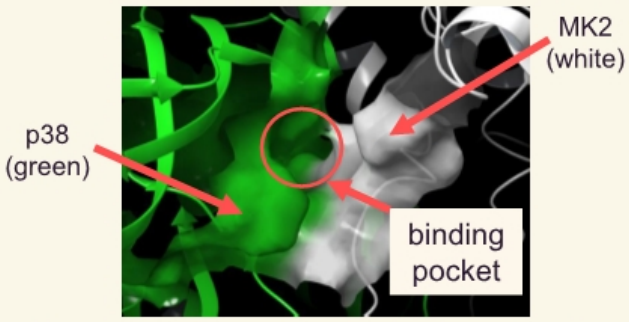
ATI-450 Blocks MK2 Activation, BUT NOT p38 Phosphorylation of Other Substrates



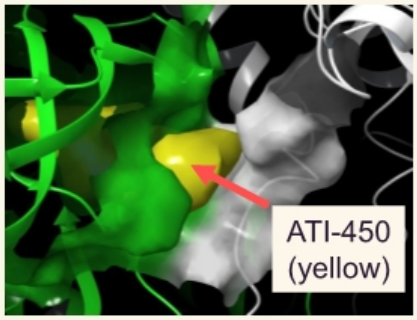
- ATI-450 “captures” MK2 in an inactive state – preventing p38MAPK from phosphorylating/activating MK2
- ATI-450 is substrate selective. It is designed to only interact with the p38-MK2 complex and not other p38 substrates

*Data on file

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

*Data on file - graphics

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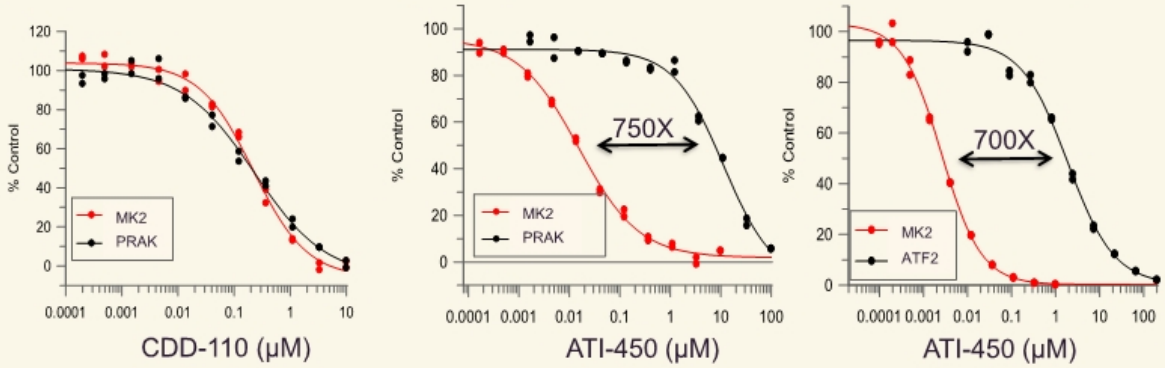
ATI-450 is Highly Selective for MK2 *vs* other p38 Substrates

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

ATI-450 inhibits MK2 ≥700X 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

PRAK = p38-regulated/activated protein kinase; MK5

*Data on file

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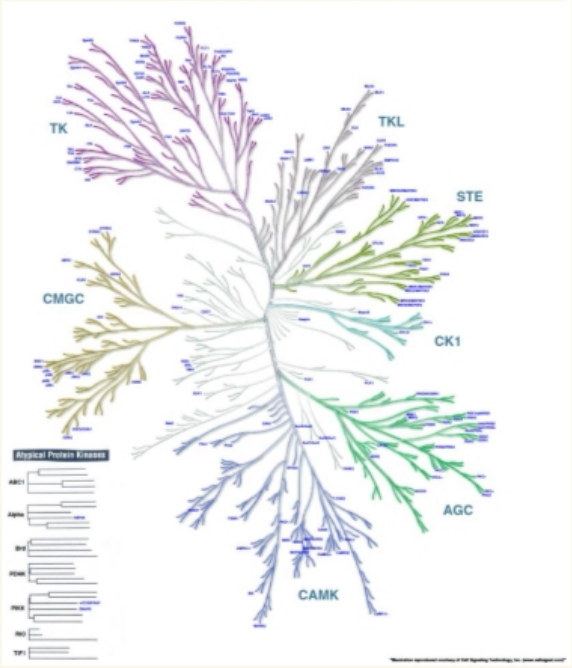
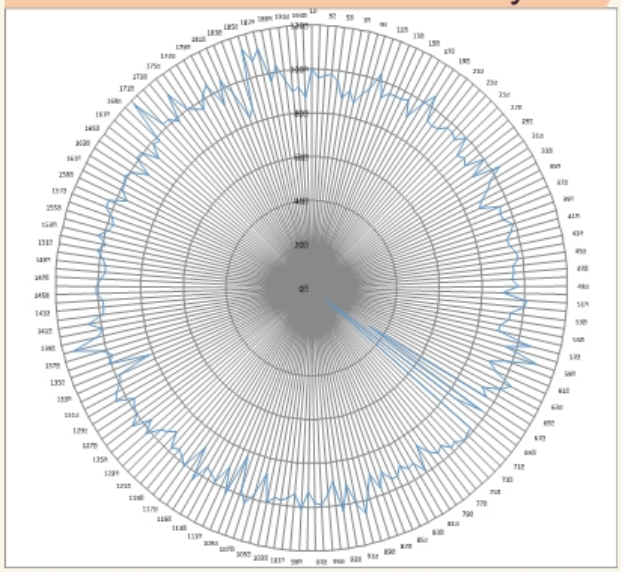
ATI-450 Selectivity

Kinase Panel



Human Kinome Selectivity



- >350-fold binding selectivity on all kinases in this panel except p38α and p38β
- In total, ATI-450 tested vs 193 kinases at 5 μM and found selective

*Data on file

ATI-450: MK2 inhibitor - Anti-inflammatory Data

(an investigational compound)

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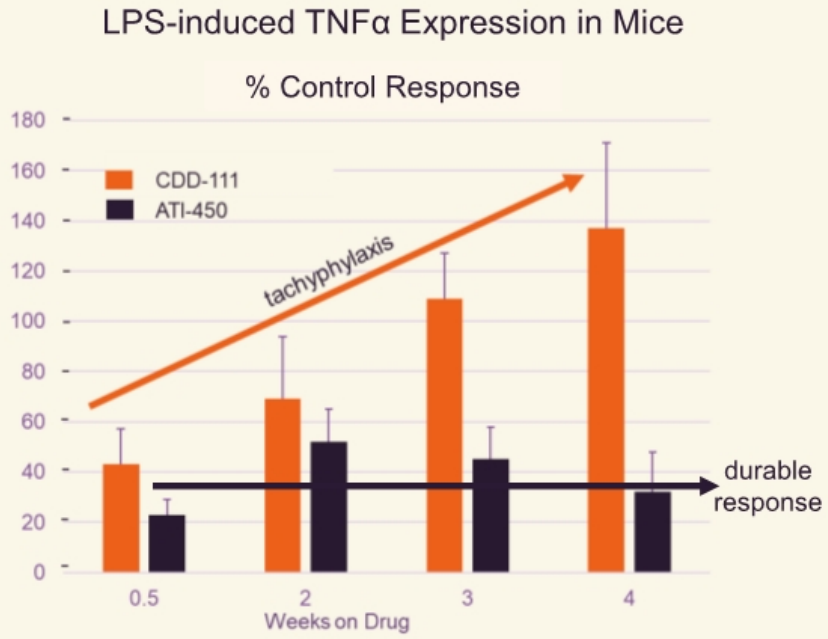
Mouse Model: ATI-450 Durable Response *in vivo*



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 TNFα 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

*Data on file

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Animal Models Supporting the Development of MK2 inhibitors in Inflammatory Diseases

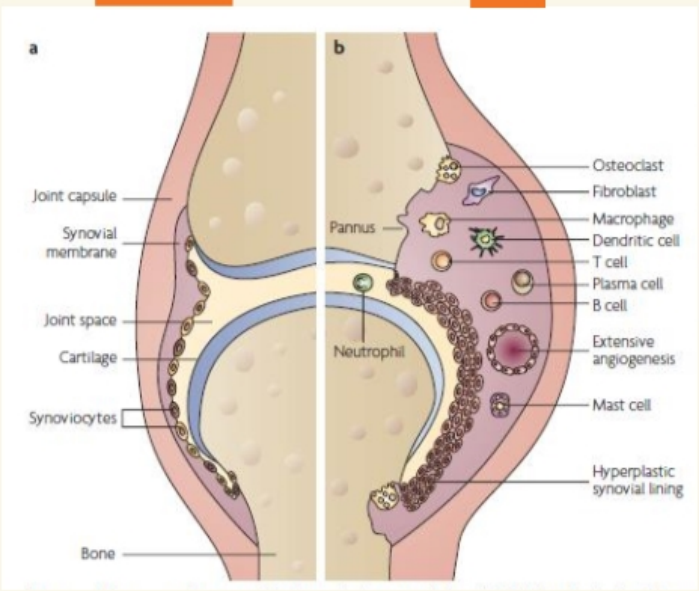
Therapeutic area	Model (all used ATI-450)	Reference
Rheumatoid Arthritis / Osteoarthritis / Psoriatic Arthritis	Rat streptococcal cell wall arthritis model - Protection against bone deterioration - Protection against lethality Inhibition of cellular IL1β mRNA stability & translation	Wang, et al., 2018, J Ex Med 215:1315
Inflammatory Bowel Disease / Crohn's	Adoptive transfer model of colitis - Endoscopy scores show disease control - Decreased inflammatory infiltrate - Protected structural integrity of mucosa	Haigis, et al., 2019 Integrative Biology, In press
Cryopyrin-Associated Periodic Syndromes (CAPS)	Murine NOMID (severe form of CAPS) transgenic model Human CAPS PBMC* IL1β 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



Nature Reviews Drug Discovery, Volume 6, 2007

Cells	Cytokines	Mediators
Monocyte/Macrophage	**TNFα**	COX-2
Osteoclast	**IL1β**	iNOS
Epithelial Cells	**IL1α**	MMP-9
Synovial Fibroblast	**IL6**	
Chondrocytes	**IL18**	
	RANKL	

*Bolded Above is ATI-450 data on file

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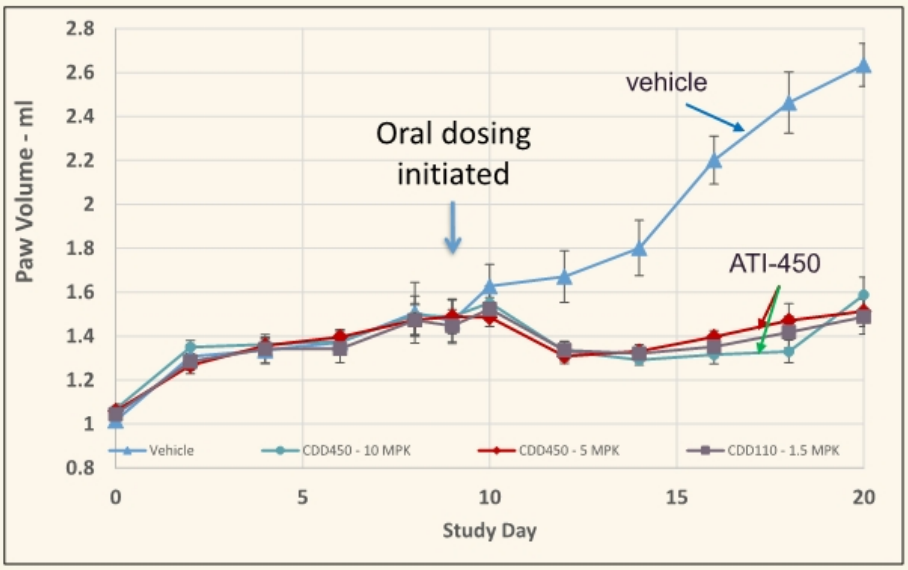
Rat Model: ATI-450 Activity in Rat Streptococcal Cell Wall Arthritis

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)

*Wang et al. 2018. J Exp Med 215:1315

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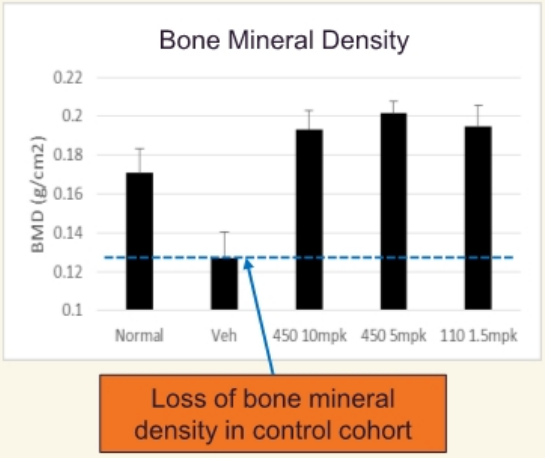
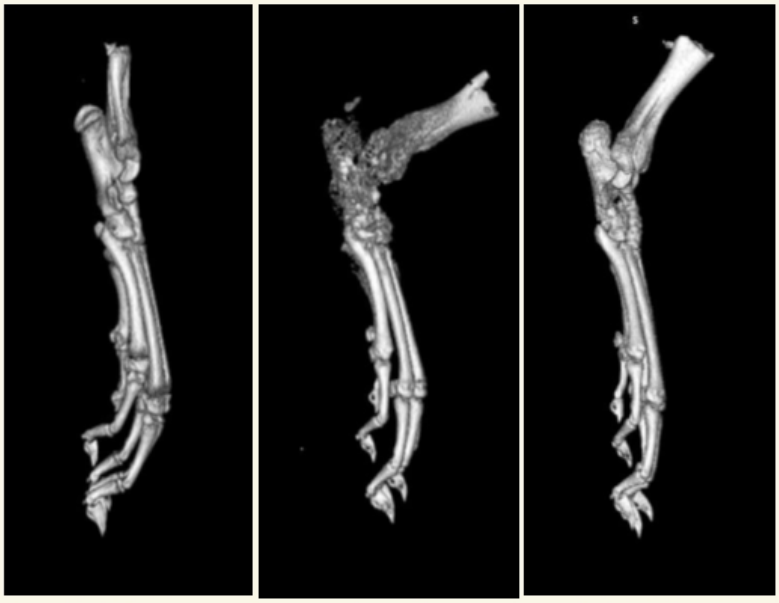
Rat Model: ATI-450 Activity in Rat Streptococcal Wall Arthritis Model: Disease Modifying Activity – Joint and Bone Preservation

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



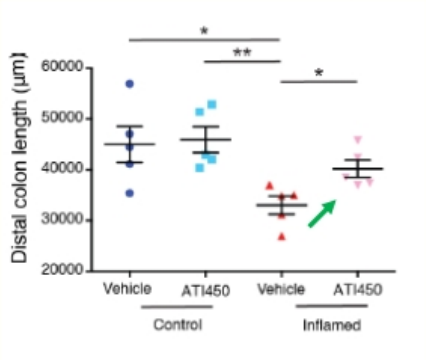


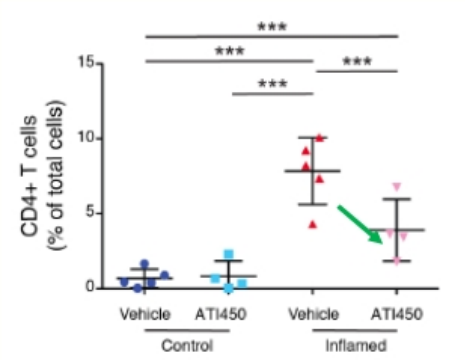
Control | Vehicle | ATI-450 (5mpk)

*Wang et al. 2018. J Exp Med 215:1315

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^{hi} T cells (naïve T cells) into RAG-1$^{-/-}$ 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)

*Strasser et al. Integrative Biology, in press - Substrate-based kinase activity inference identifies MK2 as driver of colitis.

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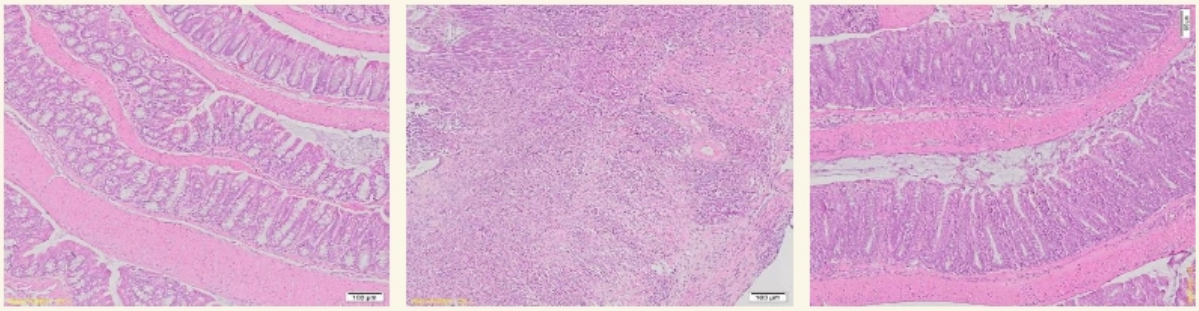
Mouse Model: Orally Dosed ATI-450 in a Crohn's Colitis Adoptive Transfer Model

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

*Strasser et al. Integrative Biology, in press - Substrate-based kinase activity inference identifies MK2 as driver of colitis.

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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
  - IL1β-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 / IL1β-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

*Wang et al. 2018. J Exp Med 215:1315

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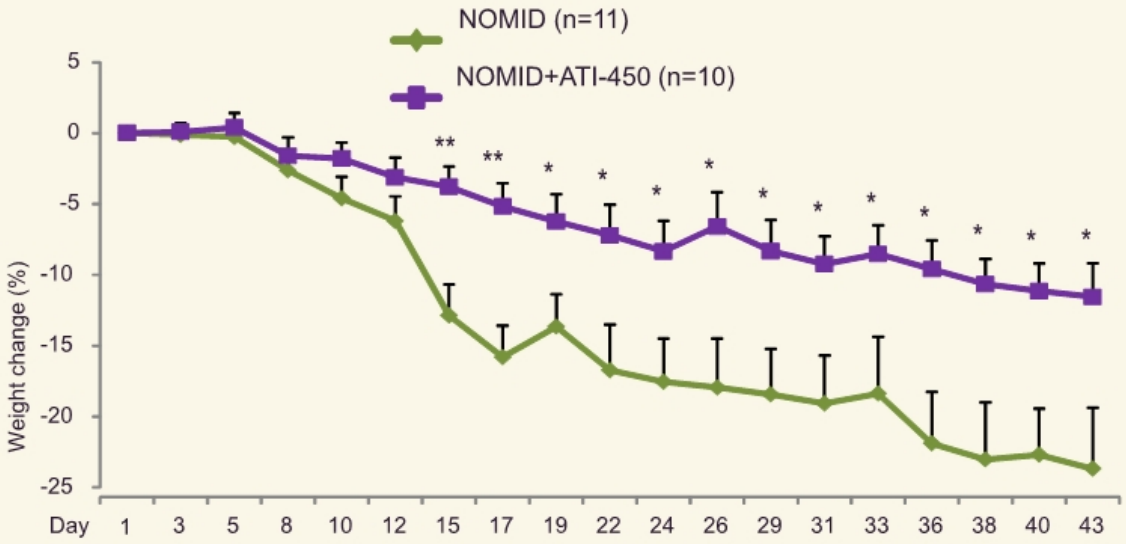
Mouse Model: ATI-450 Protects Against Weight Loss in NOMID Mice



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

*Wang et al. 2018. J Exp Med 215:1315

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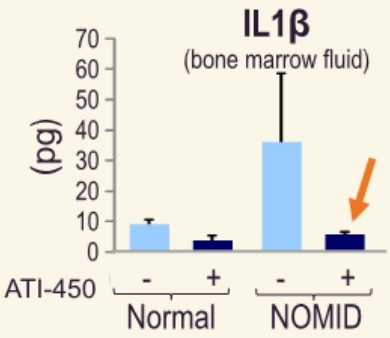
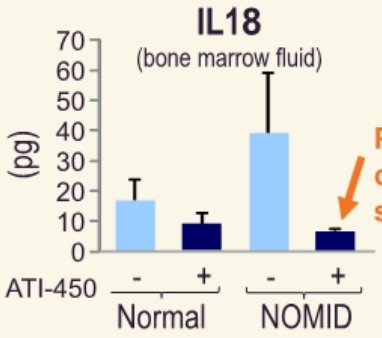
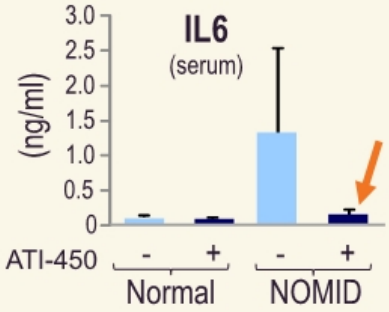
Mouse Model: ATI-450 Suppresses Inflammation in NOMID Mice





Pro-inflammatory cytokine suppression



ATI-450

PLACEBO

Orally dosed ATI-450 in NOMID mice suppresses the expression of IL1β, IL18, IL6

*Wang et al. 2018. J Exp Med 215:1315

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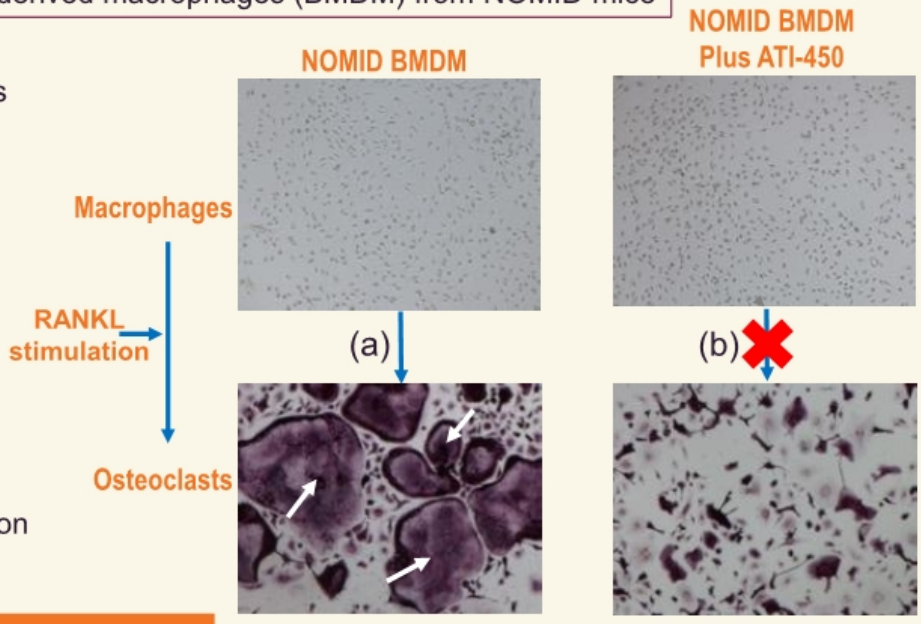
Mouse Model: ATI-450 Inhibits RANKL-induced Osteoclastogenesis

Bone marrow derived macrophages (BMDM) from NOMID mice

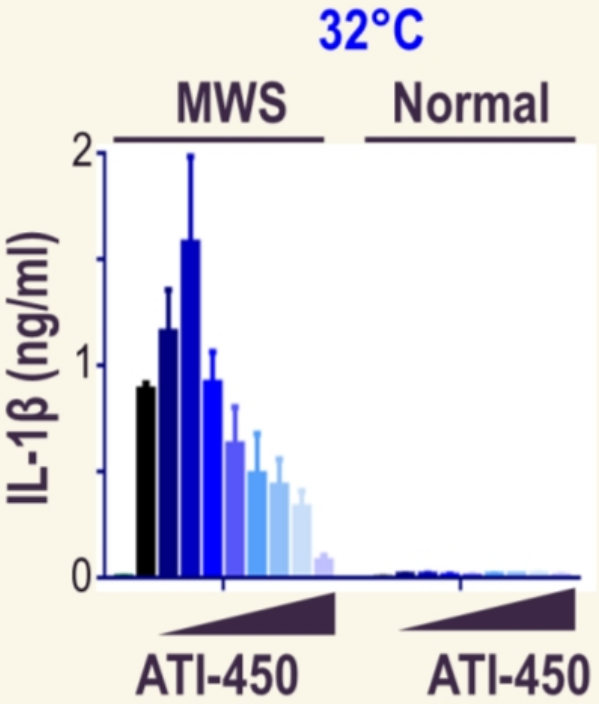
- In CAPS, osteoclastogenesis gives rise to low bone mass (osteopenia)
- (a) When bone marrow derived macrophages (BMDM) from NOMID mice are stimulated with RANKL (RANK ligand), they differentiate into osteoclasts
- (b) ATI-450 blocks this macrophage differentiation



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

*Wang et al. 2018. J Exp Med 215:1315

Ex Vivo Data: ATI-450 Inhibits IL1β 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 IL1β expression) is triggered by exposure to low temperatures.
- CAPS PBMCs spontaneously produced high amounts of IL1β at 32°C but not at 37°C.
- ATI-450 blocks stress induced IL1 beta production.

*Wang et al. 2018. J Exp Med 215:1315

ATI-450: MK2 inhibitor - Development Status and IND-Related Studies

(an investigational compound)

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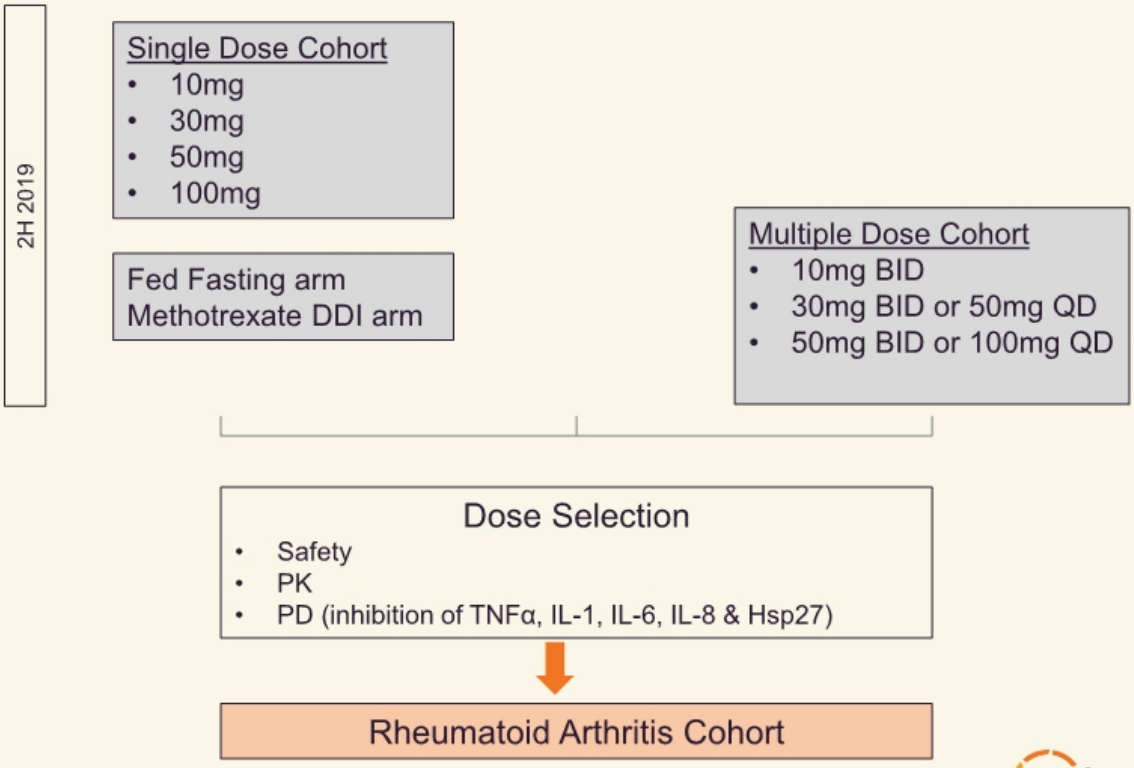
ATI-450 IND Status

- 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

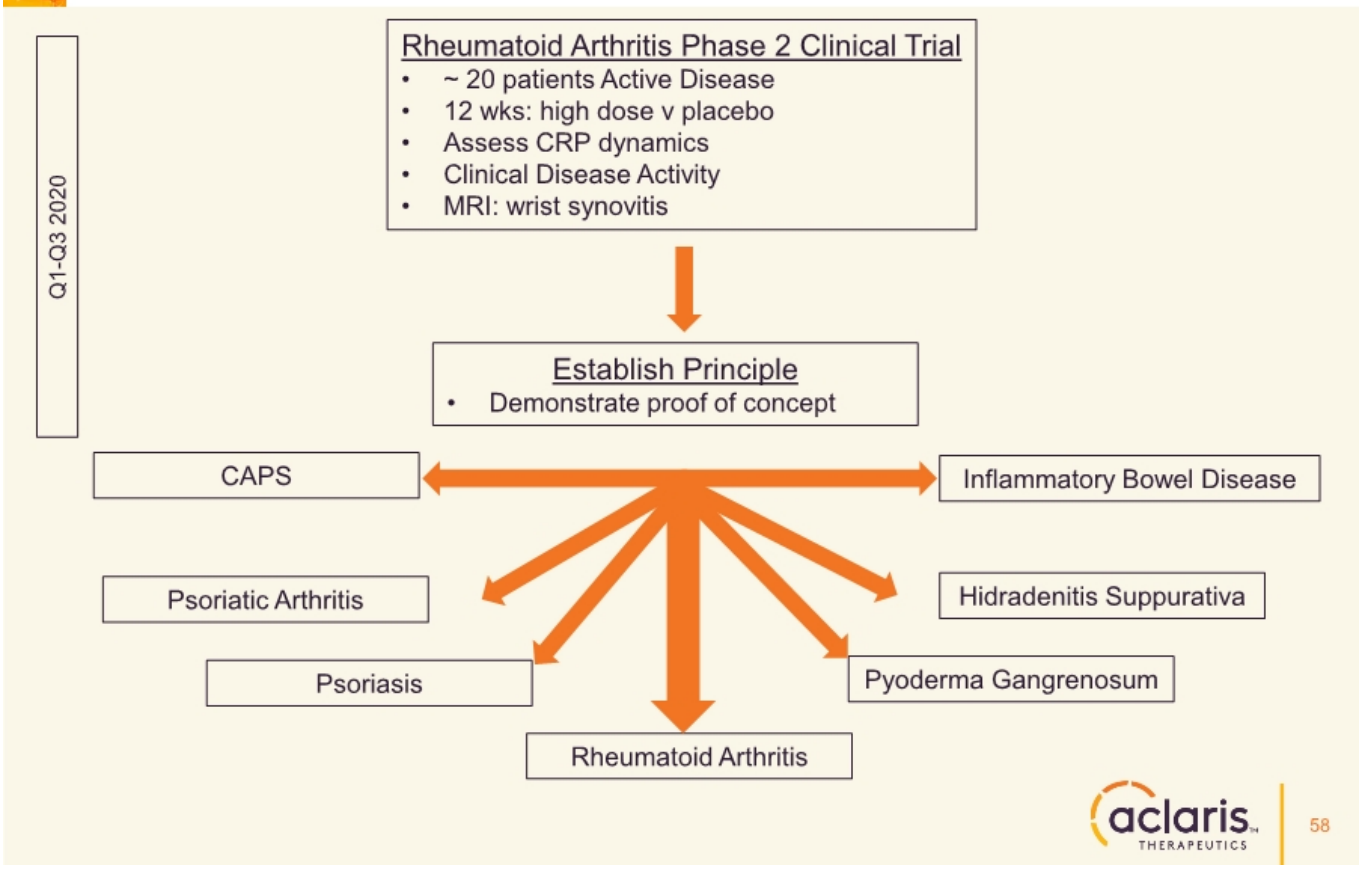
ATI-450 Pharmaceutical Development

- 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



ATI-450: MK2 inhibitor in Oncology

(an investigational compound)

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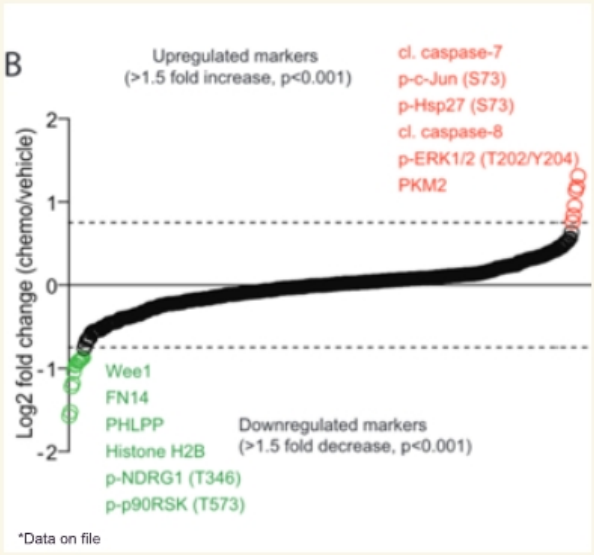
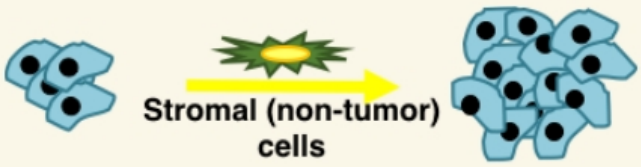
ATI-450 in Oncology – Dual Mechanisms



Pancreatic Cancer

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



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

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

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

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

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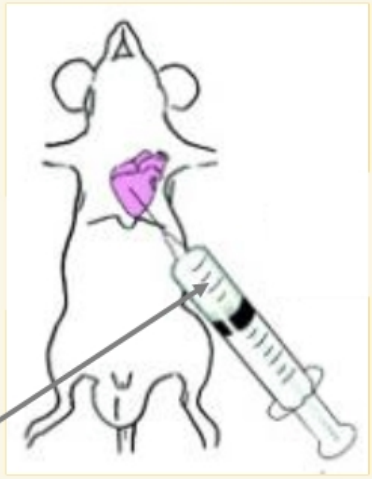
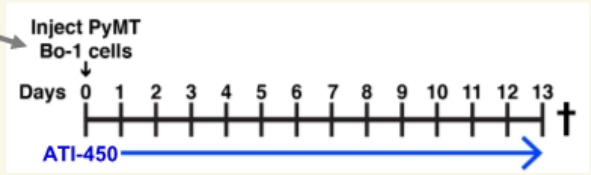
Modeling Bone and Visceral Metastasis in the Mouse

- 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 [1]
- Bo-1 PyMT metastatic breast cancer cell line 2[2]

Intra-cardiac tumor cell injection model





[1] 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
[2] Su et al_2016.Antagonizing integrin β3 increases immunosuppression in cancer. Cancer Res 76(12):3484

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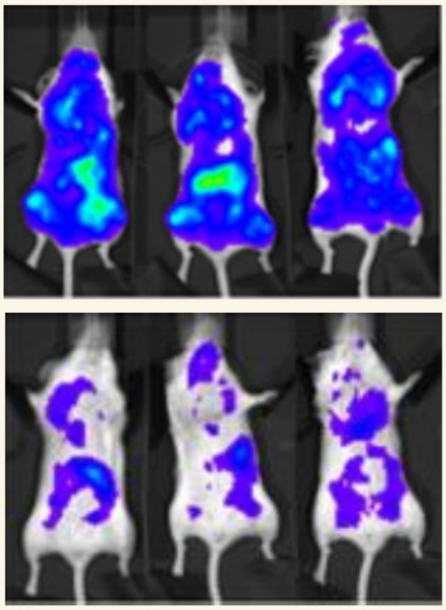
Mouse Model: ATI-450 Reduces Visceral Organ Tumor Burden

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**

*Stewart lab / Murali et al. 2018. Inhibition of the stromal p38MAPK/MK2 pathway limits breast cancer metastases and chemotherapy-induced bone loss. Cancer Res 78:1

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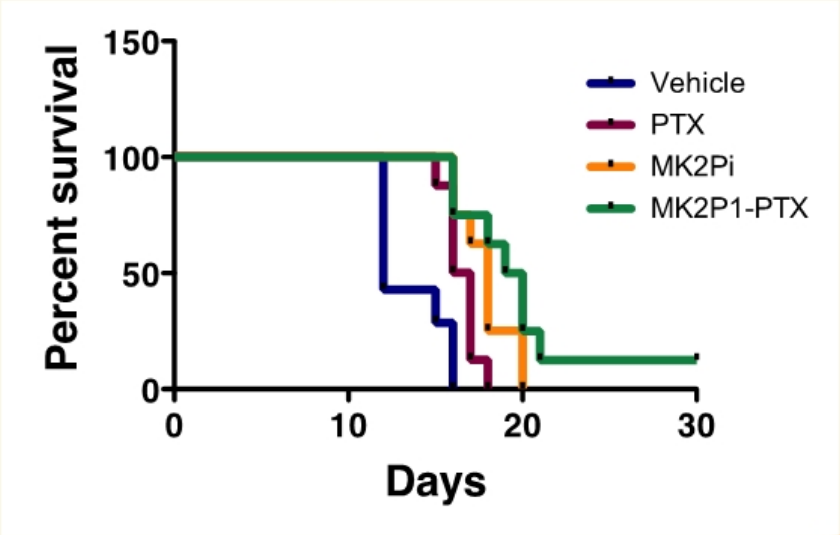
Mouse Model: ATI-450 and Paclitaxel (PTX) Increases Overall Survival

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



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

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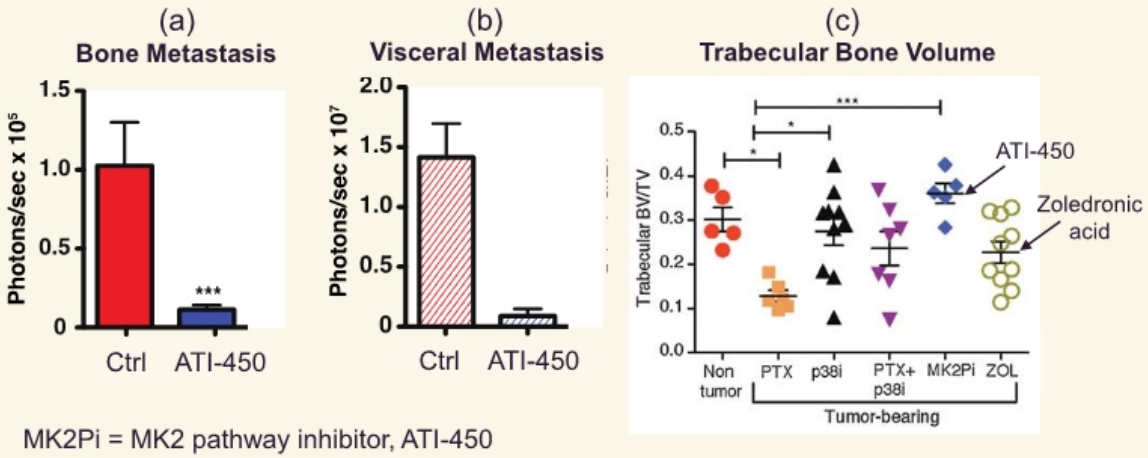
Mouse Model: ATI-450 Reduces Metastases *and* Preserves Bone

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)

*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

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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

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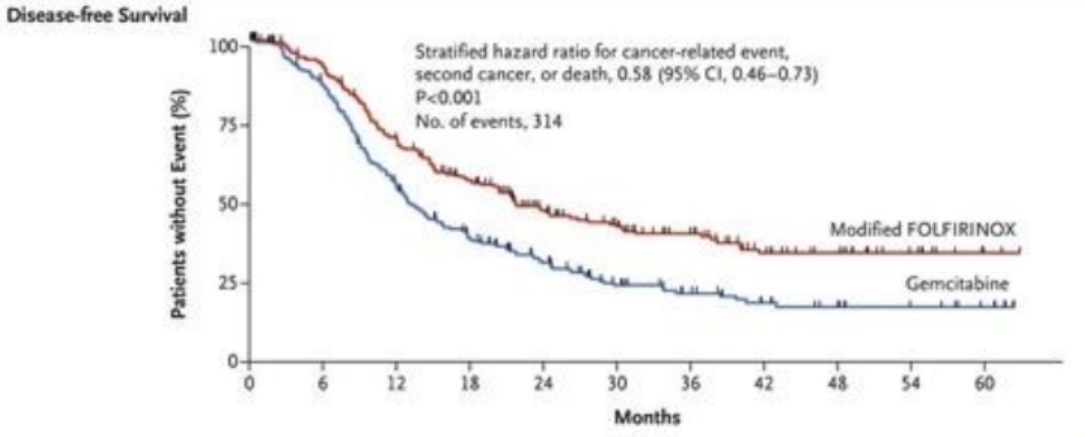
ATI-450 Pancreatic Cancer Update



- SOC for PDAC is switching from gemcitabine to FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, oxaliplatin)[1]
- 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?

[1] Conroy et al., NEJM 379:2395, 2018

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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:[1]
  - 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:[1]
  - 5FU 50mg/kg
  - Irinotecan 6.7mg/kg
  - Oxaliplatin 35mg/kg
- Low dose FOLFIRINOX is 1/2 the high dose for each component

1 J Morton et al, 246–251 PNAS January 5, 2010 vol. 107 no. 1 www.pnas.org/cgi/doi/10.1073/pnas.0908428107

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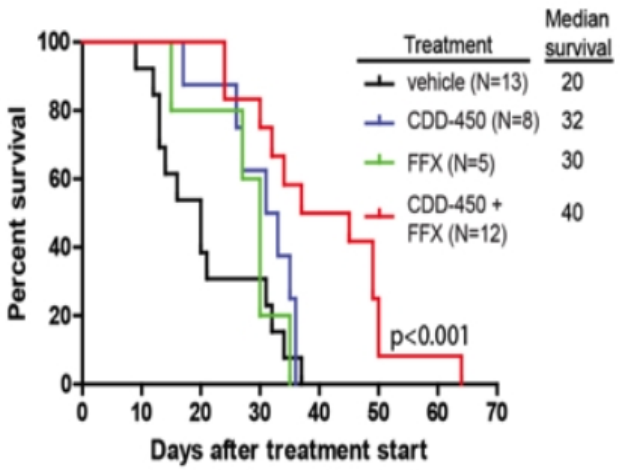
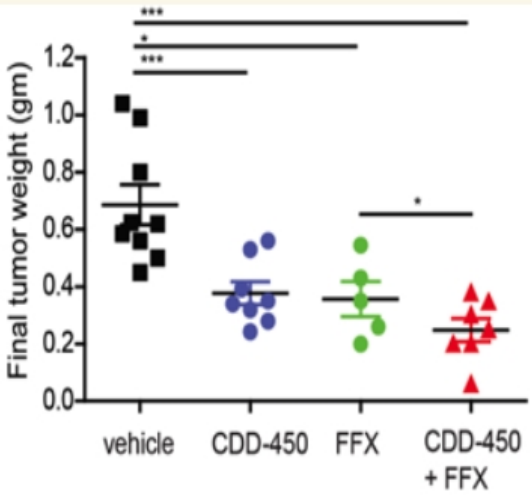
Combination of ATI-450 and Folfirinox Improves Efficacy in Autochthonous Mouse Model of Pancreatic Cancer (KPPC)





- 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

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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)

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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[1]
  - 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

1 R Shreberk-Hassidim, Et Al Janus kinase inhibitors in dermatology: A systematic review, J Am Acad Dermatol. 2017 Apr;76(4):745-753.

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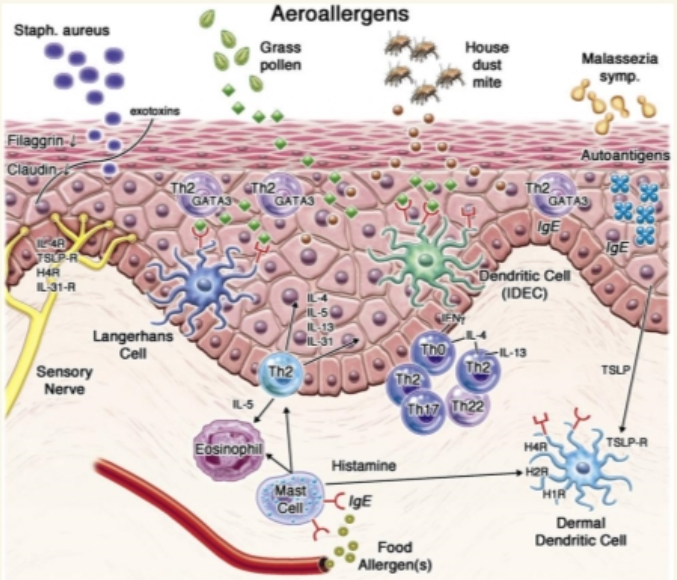
Designing a Drug Physicians and Patients May Prefer

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%[1]
- 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[2]
- 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



WERFEL ET AL; J ALLERGY CLIN IMMUNOL AUGUST 2016; 340

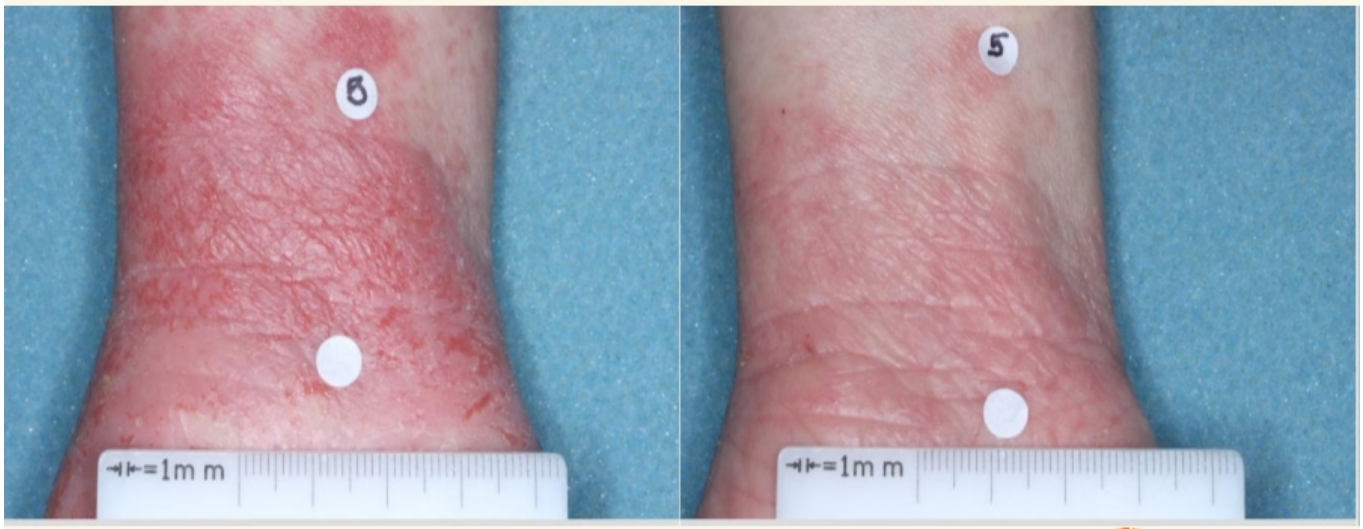
Topical ATI-1777 has a high probability of demonstrating efficacy and safety in AD

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

2 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

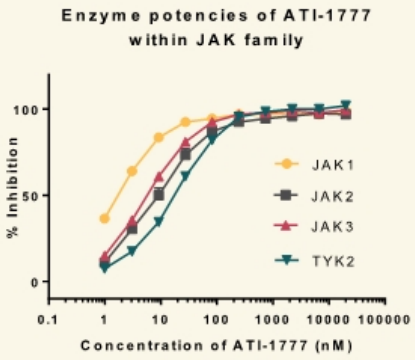
- ATI-502 Topical Solution, 0.46% (not soft)
- Patients with Moderate to severe AD: Physician Global Assessment (PGA) 3/4
- 28 days open label treatment
- 17 completers: 7/17 (41.2%) achieved PGA ≤ 1 (at least 2-point change)

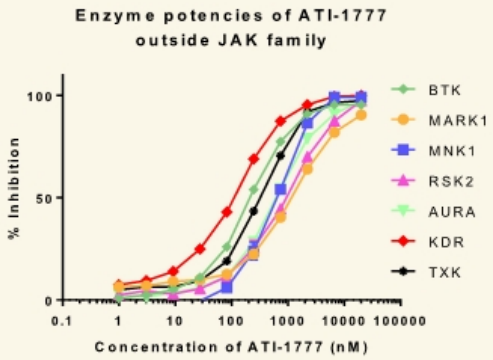


Designing a Better Topical Drug for Atopic Dermatitis

- ✓ 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_{50}, nM)										
JAK1	JAK2	JAK3	TYK2	BTK	MARK1	MNK1	RSK2	AurA	KDR	TXK
1.5	**7.1**	**3.8**	**19**	210	1250	584	1050	641	127	351

The kinome selectivity of ATI-1777 was evaluated against 194 kinases as 5μM at LifeTech. IC_{50} values were generated at K_m ATP concentrations on those kinases that inhibited ≥80% at 5μM.

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

*Data on file

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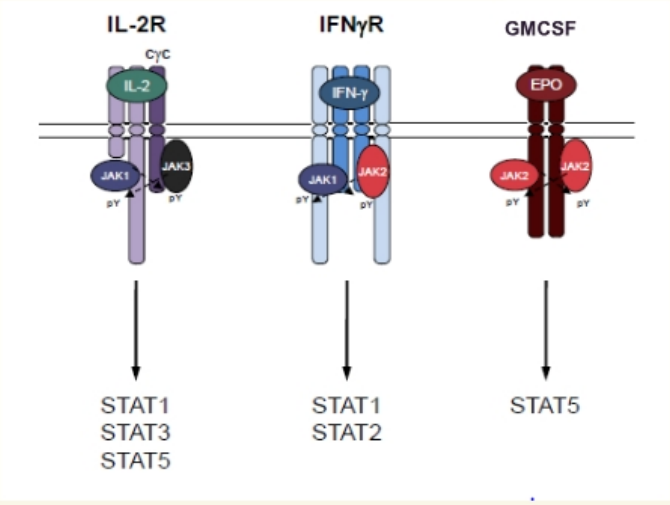
Cellular JAK/STAT Assays



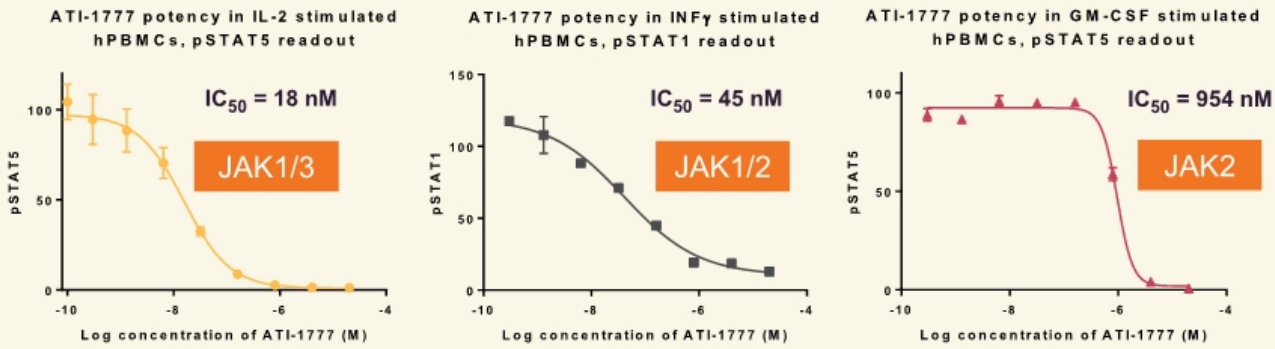
Cytokine	JAKs	STAT
IL-2 / IL-15	JAK1/3	STAT5
IFNγ	JAK1/2	STAT1
GM-CSF	JAK2	STAT5

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
- IFNγ 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

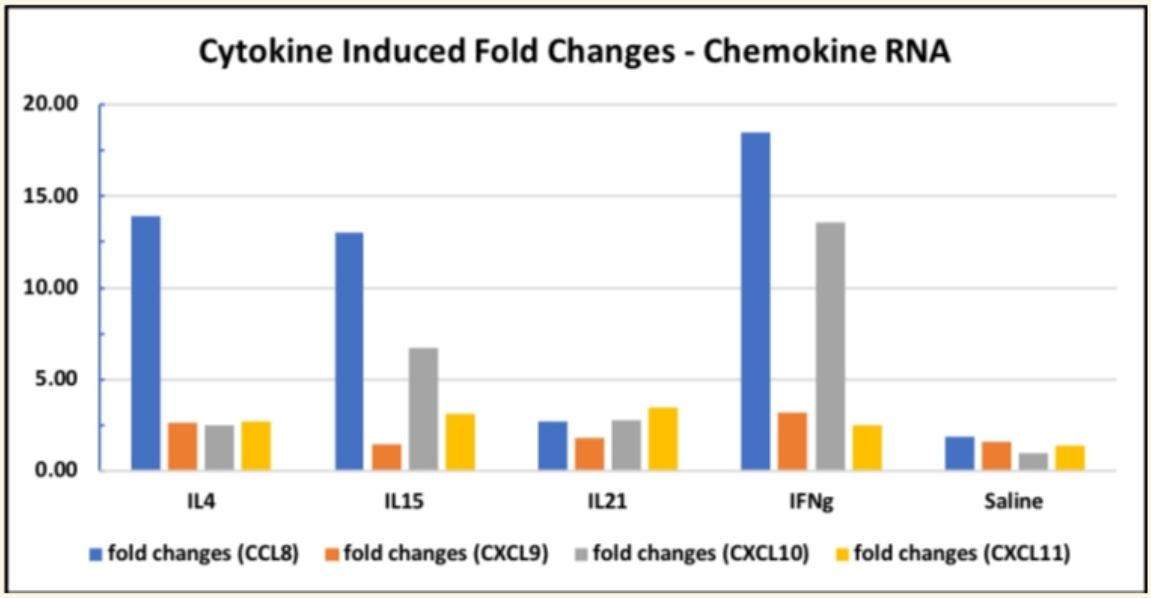
Functional selectivity assessed by stimulating hPBMCs with IL-2 (STAT5), IFN-γ (STAT1), and GM-SCF (STAT5) - measuring IC_{50}s for inhibiting P-STAT generation



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

*Data on file

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

*Data on file

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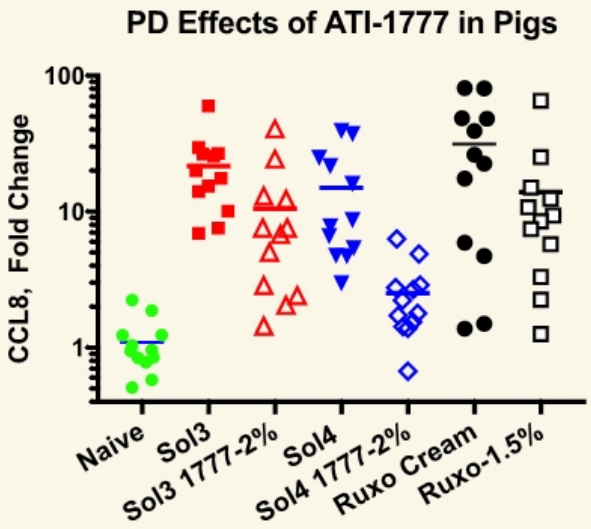
Porcine Model: ATI-1777 in Two Formulations Blocked IL-15 Induced CCL8



Formulation	P value	% Decrease
Solution 3	0.0460	52
Solution 4	**0.0031**	**83**
Ruxo Cream	0.0831	56

*Data on file

- 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)

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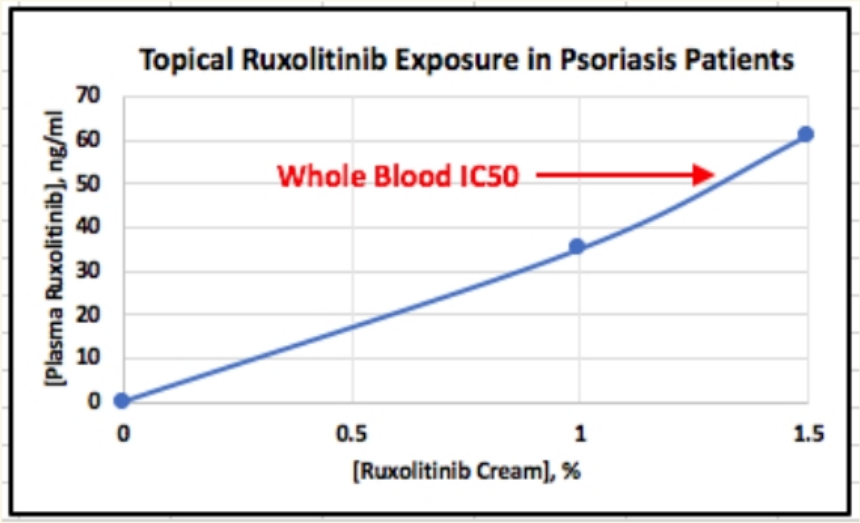
Clinical Ruxolitinib Systemic Exposure After Topical Application



- 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**[1], as high as **191 nM**.
  - Ruxolitinib whole blood IC50 (**red line**) is **~50 nM**[2] – **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

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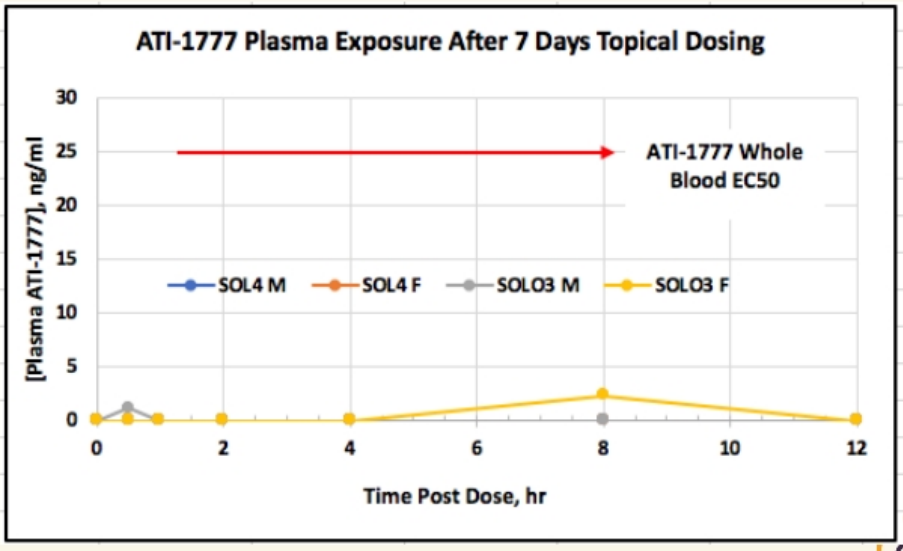
Minipig Model: ATI-1777 Nonclinical Safety Program TK Data

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



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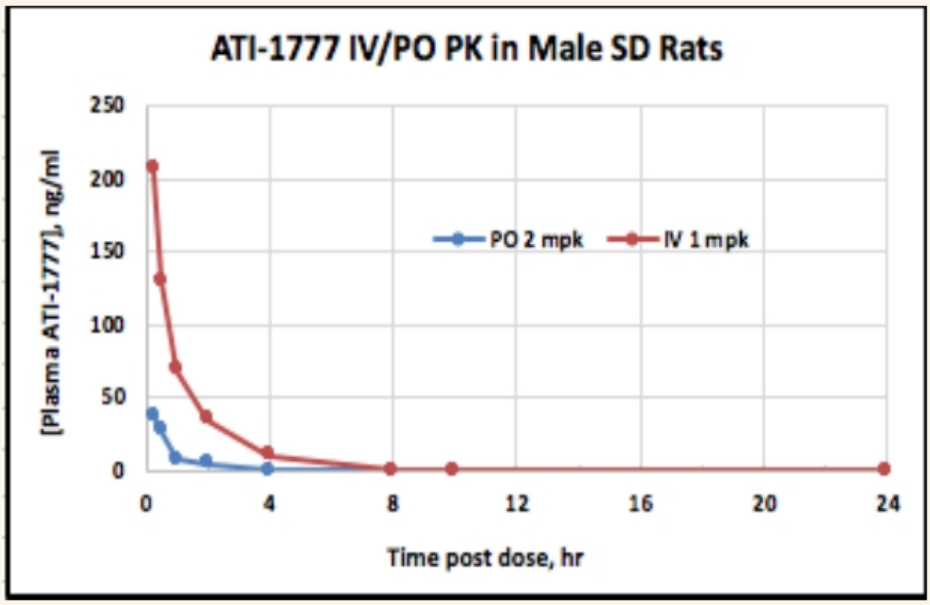
Rodent Model: ATI-1777 *In Vivo* PK Properties



- 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

*Data on file

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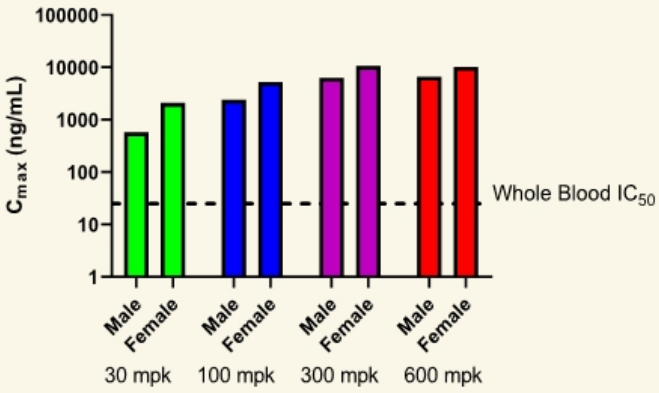
Rodent Model: ATI-1777 Nonclinical Safety Program

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

ATI-1777 Day 1 mean plasma C_{max} in SD rats after oral dosing



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 ≥ 600 mg/kg/day
- This resulted in Cmax = 7680 ng/mL, and AUC0-t = 42,700 ng*h/mL for males on Day 7, respectively

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

*Data on file

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)

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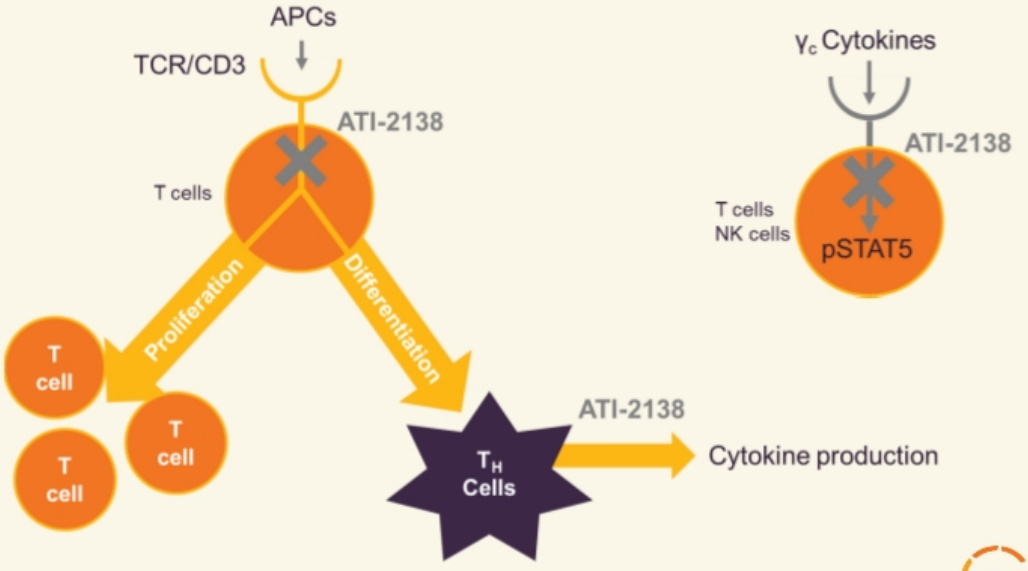
ATI-2138: ITK/TXK/JAK3 Inhibitor for Autoimmune Disease

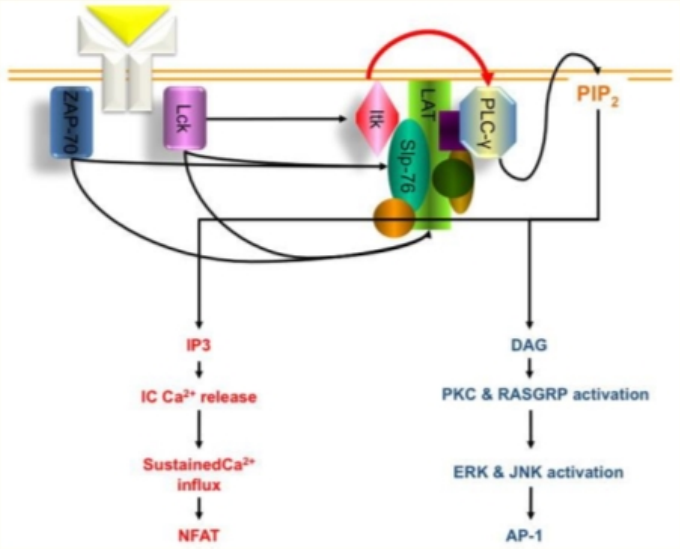
- ATI-2138 is an investigational oral compound which interrupts T cell receptor (TCR) signaling and cytokine signaling in lymphocytes
- Evaluating for the potential treatment for a number of T cell mediated autoimmune diseases



ITK/TXK Function and Expression

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

ITK and TXK regulates the T cell receptor

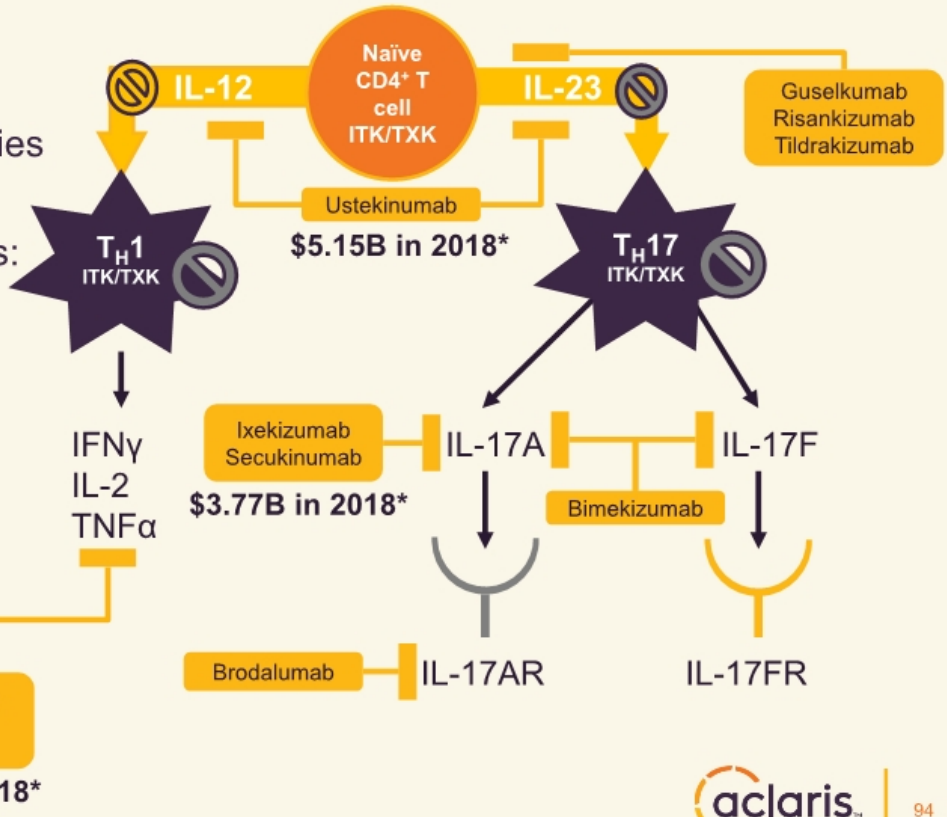


Prince, A.L. et al., *Immunological Reviews* **2009**, *228* 115–131

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

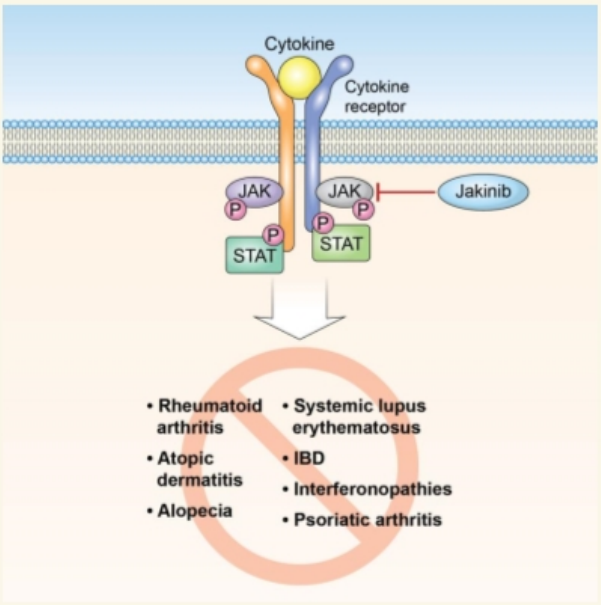
ATI-2138: Impacts Clinically Important Pathways

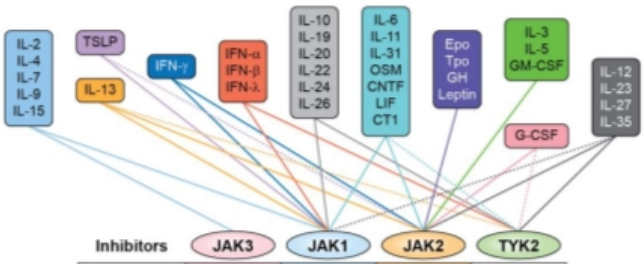
- ATI-2138 function is analogous to IL-12/23/17 antibodies
- Potential Indications:
  - Psoriasis
  - Psoriatic arthritis
  - IBD
  - Ankylosing spondylitis



*Annual Sales Data from Factset

JAK signaling and JAK inhibitors





Inhibitors	JAK3	JAK1	JAK2	TYK2
Tofacitinib	×	×	×	
Ruxolitinib		×	×	
Baricitinib		×	×	
Peficitinib	×	×	×	
Momelotinib			×	
Fedratinib			×	
Filgotinib		×		
Upacitinib		×		
Itacitinib		×		
PF-06651600	×			
BMS-986165				×
PF-06700841		×		×

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

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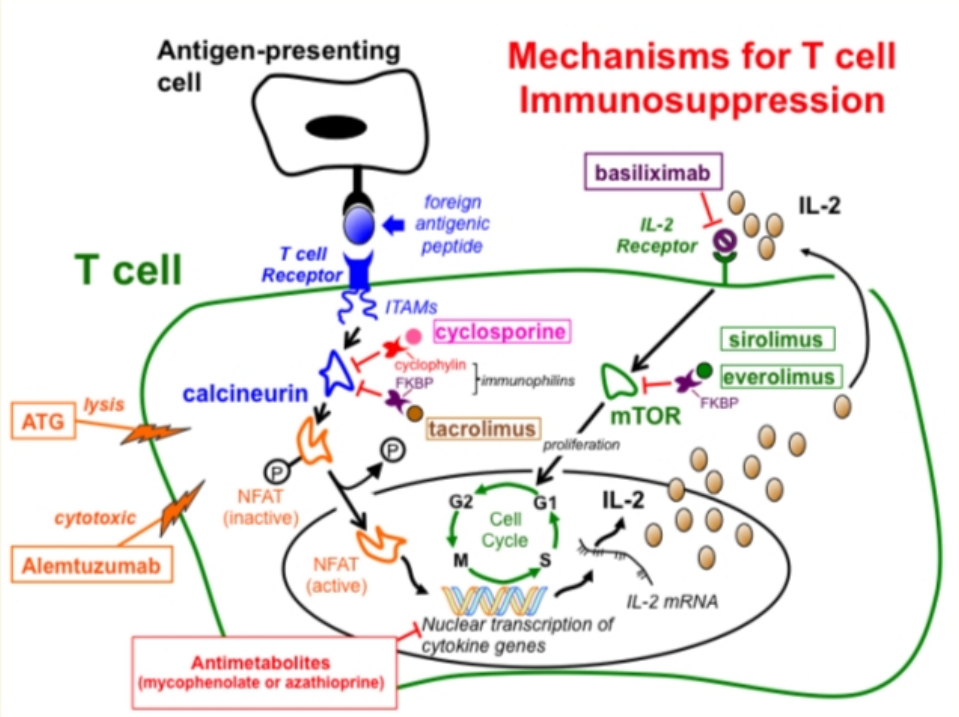
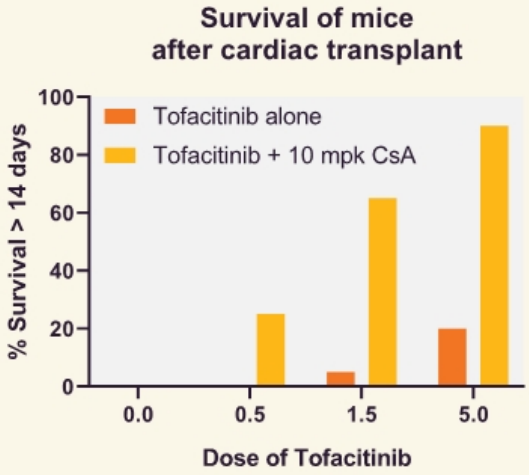
Examples from the Organ Transplant Field



- 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 αIL-2R)
- ITK/TXK inhibitors will block T cell receptor and JAK3 inhibitor will block IL-2R
- By virtue of blocking ITK/TXK 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



- 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

Kudlacz et. al., *Am. J. Transplantation*, **2004**, *4*, 51

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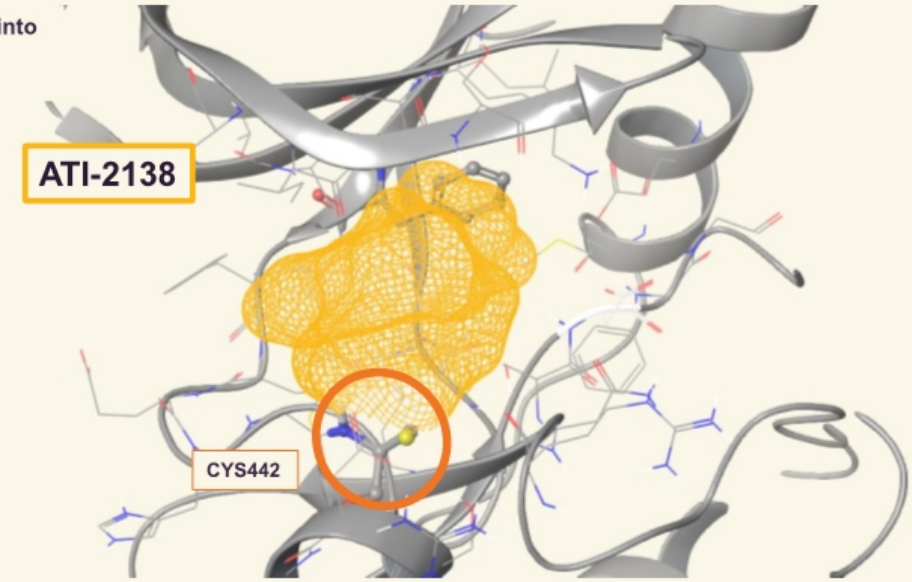
Pre-clinical Data: ATI-2138 Covalently Inhibits ITK, TXK and JAK3

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 cystine in kinases
  - Ibrutinib (BTK)
  - Afatinib, Neratinib (EGFR/Her2)
  - PF-06651600 (JAK3)

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ATI-2138: Activity in Enzyme Based Assays

Kinase	IC_{50} (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 1μM
- IC_{50} 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*

*Data on file

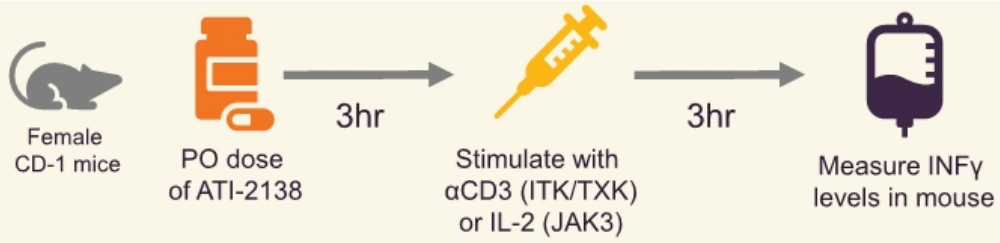
Pre-clinical Data: ATI-2138 Activity in Cell Based Assays

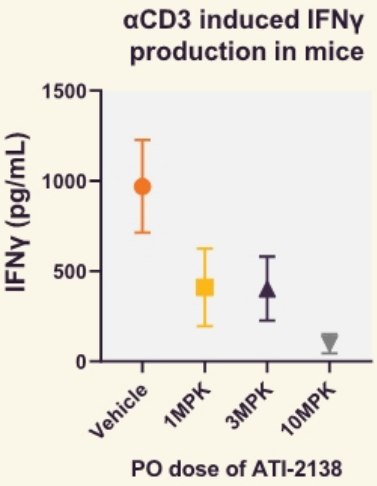
Assay	ATI-2138 (μM)	Assay Description
hJurkat pPLCγ-1 IC_{50}	0.007	Assesses ITK/TXK activity
hPBMC pSTAT-5 IC_{50}	0.02	Assesses JAK1/3 activity
Ramos pPLCγ-2 IC_{50}	0.052	Assesses BTK activity
HWB αCD3/IL15 IFNγ IC_{50}	0.013	Assesses both ITK/TXK and JAK3 pathways

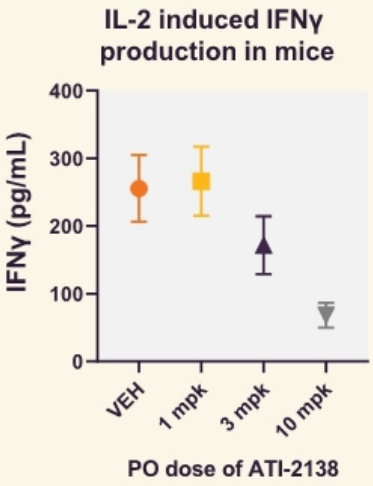
ATI-2138 potently inhibits ITK/TXK and JAK3 in cells and in whole blood

*Data on file

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



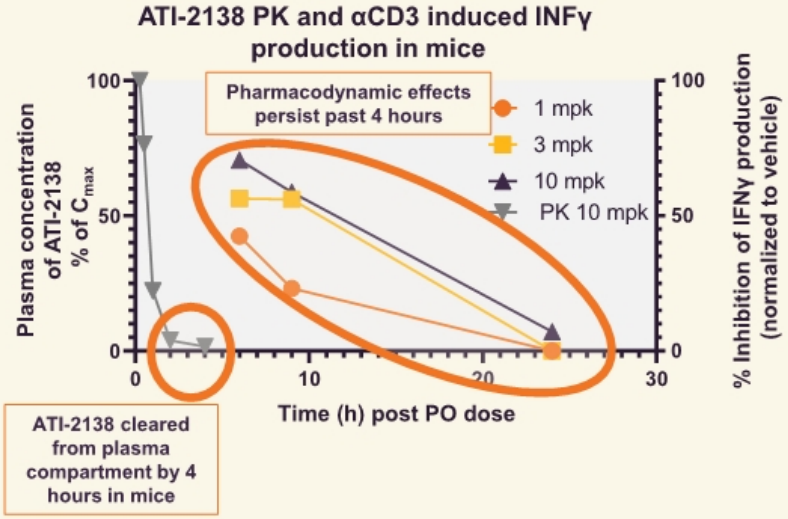




- ATI-2138 potently inhibited TCR signaling *in vivo*
- At higher doses can inhibit both TCR and JAK3 pathways

*Data on file

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



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

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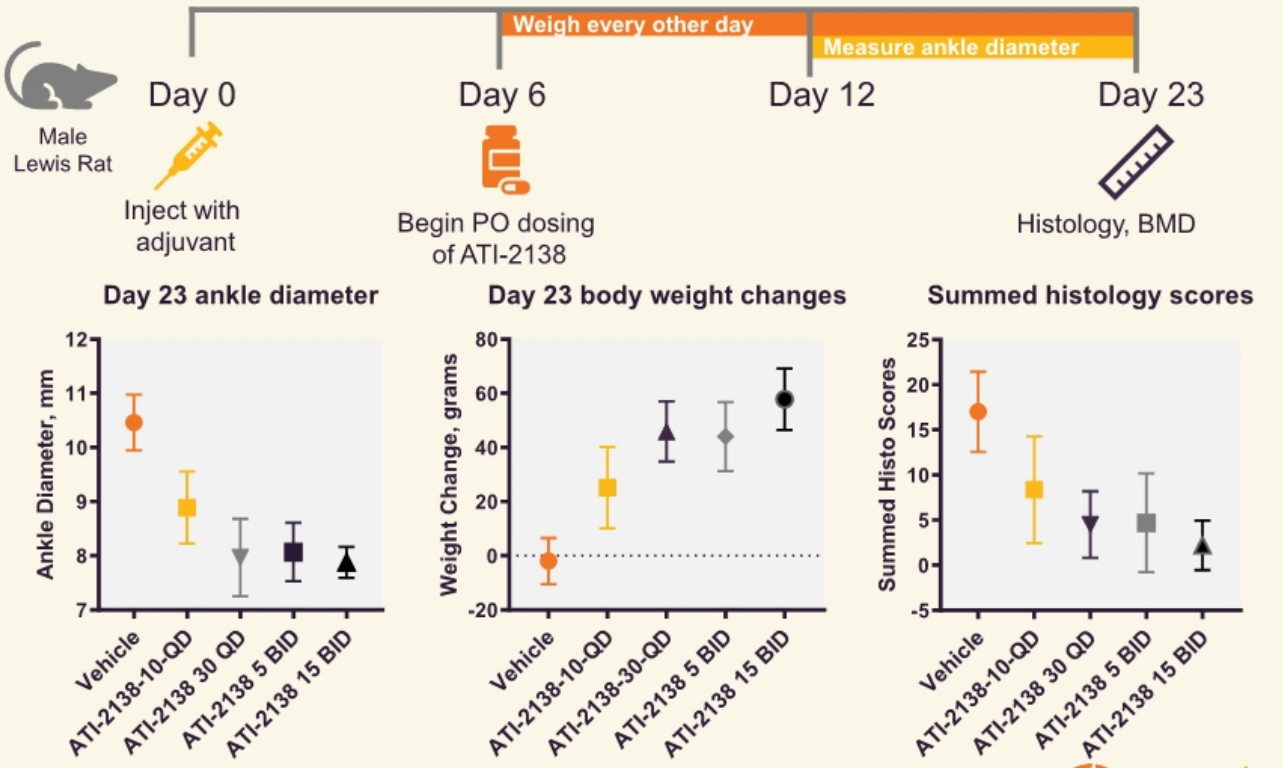
Rat Model: ATI-2138 Demonstrated Activity in Rat Adjuvant Induced Arthritis (AIA) model



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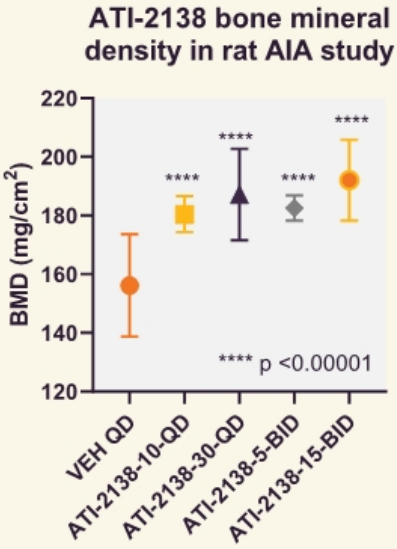
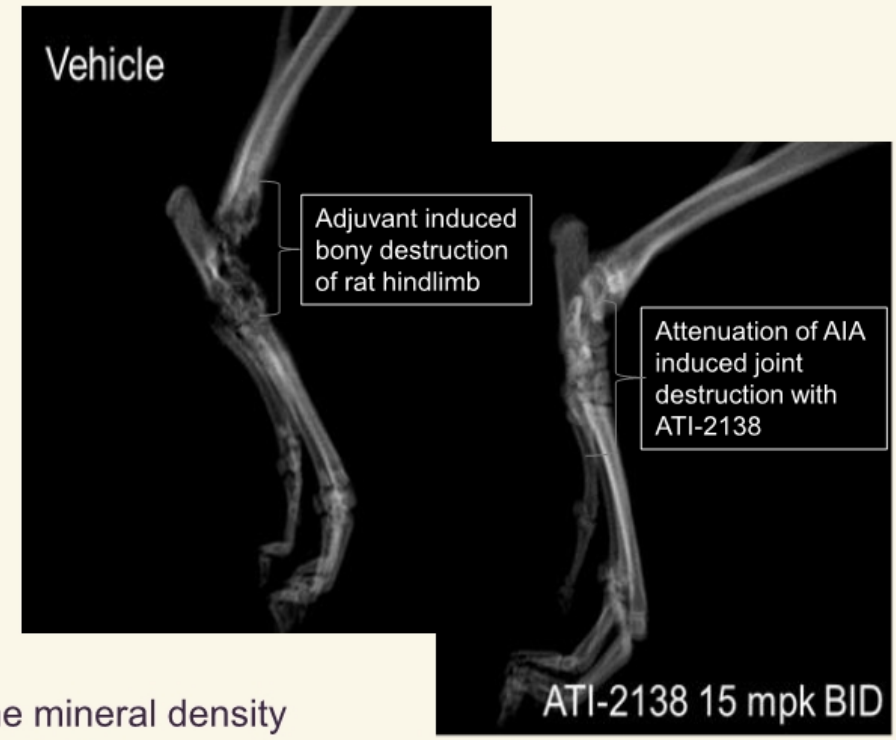
Rat Model: ATI-2138 Protected Bone in the Rat Adjuvant Induced Arthritis AIA Disease Model

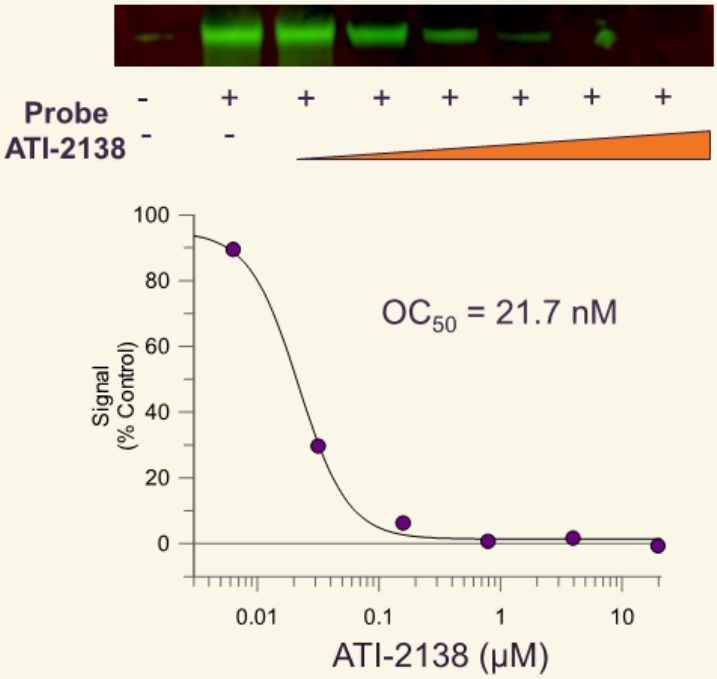




- ATI-2138 reduced bone mineral density loss in rat AIA disease model

*Data on file

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
- OC_{50} – concentration of an inhibitor at which 50% of its target is occupied

*Data on file

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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.[1]
    - 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

1 Factset Drug sales data

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[1]
- Little public data about JTE-051, but appears selective for ITK in enzyme and weakly potent in cell assays based on published data[1]
- ATI-2138 has inhibited both ITK and TXK

[1] Xu et. al., ACS Chem. Biol. 2019, 14, 1235

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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/TXK 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

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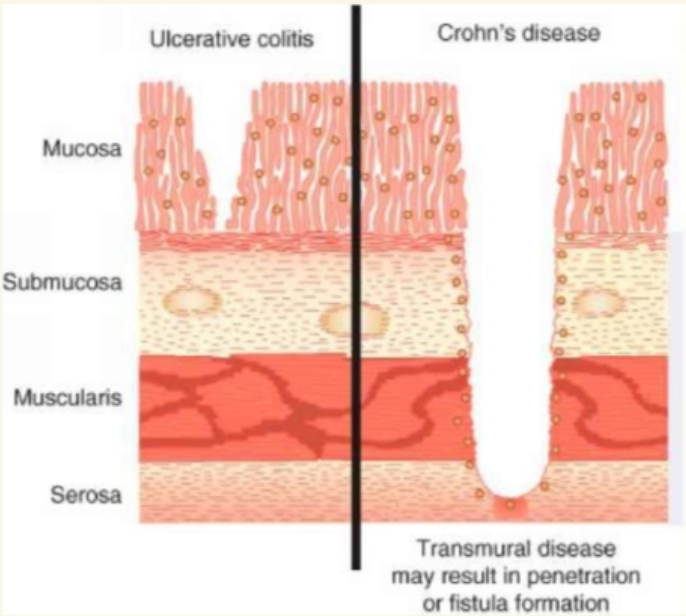
Inflammatory Bowel Diseases (IBD)

- IBD: Ulcerative colitis (CD) 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

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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/TXK/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, IFNγ, etc.)

Progress to Gut-Restricted IBD Drug

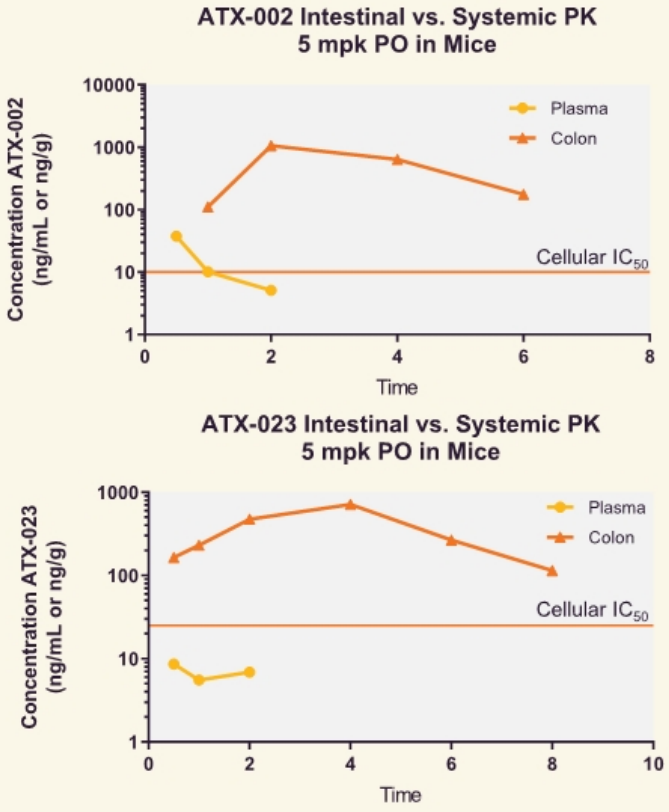
- Identify potent covalent JAK3/ITK and reversible JAK inhibitors
  - Covalent ITK/JAK3 ATX-002 and ATX-001 (investigational compounds) in hand √
  - Reversible pan-JAK1 ATX-025 (non-covalent JAK inhibitor) and ATX-023 in hand √
  - Initial studies were done with ATX-002 and ATX-025
- Show compounds 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**	**IFNγ**	**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 (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_{50} 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

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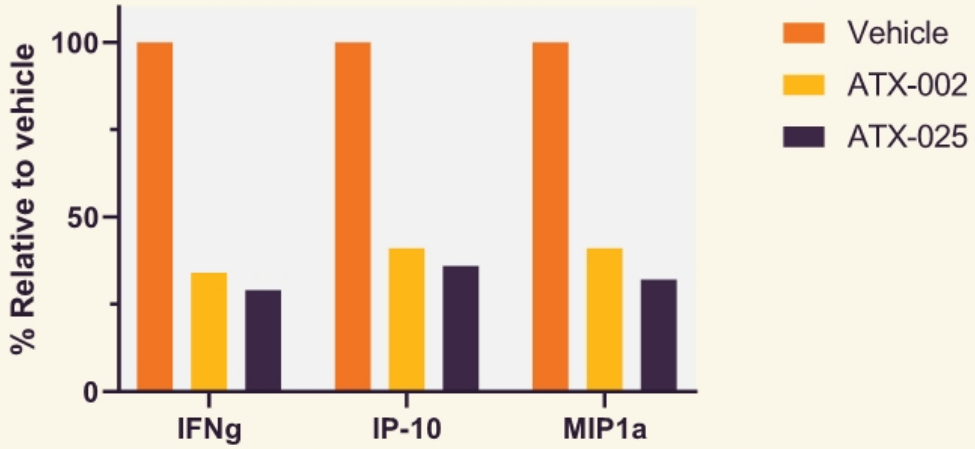
Mouse Model: ATX-002 and ATX-025 Inhibit OXA Induced Cytokines

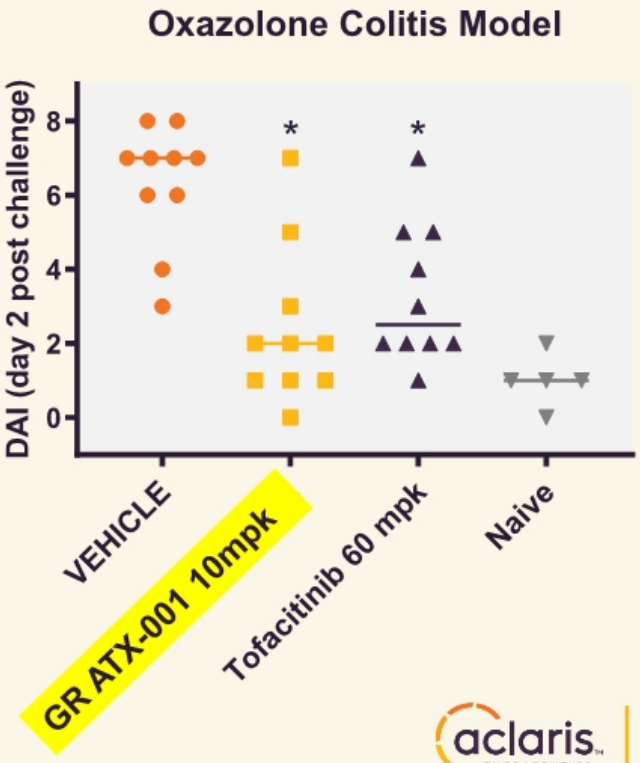
Oxazolone PD Model - Cytokine Inhibition



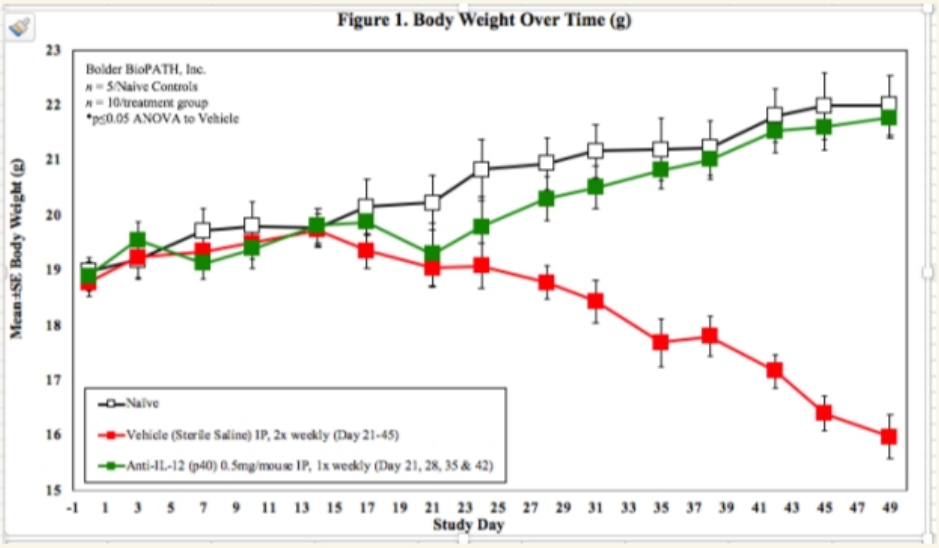
- Shaved mice primed topically with 4% oxazolone. Seven days after priming:
  - 0 hr: Mice dosed PO with ATX-002 or ATX-025, 30 mg/kg
  - 2 hr: Mice injected intrarectally with 100 ml, 1% OXA
  - 4 hr: Colons harvested, and lysate analyzed cytokines by ELISA (MSD)
- 3 cytokines significantly inhibited after oral dosing with compound and OXA intrarectal challenge
  - **IFNγ, IP10 and MIP1α**

Mouse Model: Oxazolone Model of Colitis

- Standard model of oxazolone induced colitis performed with ATX-001 which is an ITK/JAK3 inhibitor
  - Day 0 – Topical Oxa prime
  - Day 5 - Begin PO dosing, BID
  - Day 6 – IR Oxa challenge
  - Days 7 and 8 in-life DAI scoring
  - Terminal histology
- DAI (Disease activity index)
  - Body weight
  - Stool consistency
  - Stool blood
- Significant differences in DAI (*)
- **Gut Restricted ATX-001 demonstrated positive results comparable to systemically available tofacitinib**



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

*Data on file – Bolder Biopath

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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 (αIL-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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REVELATIONARY
SCIENCE

THANK YOU

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