

EMPOWERING PATIENTS THROUGH
KINOME INNOVATION

Company Overview

June 2020



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Any statements contained in this presentation that do not describe historical facts may constitute forward-looking statements as that term is defined in the Private Securities Litigation Reform Act of 1995. These statements may be identified by words such as "believe," "expect," "may," "plan," "potential," "will," and similar expressions, and are based on Aclaris' current beliefs and expectations. These forward-looking statements include expectations regarding Aclaris' development of its drug candidates, including the timing for initiation and completion of clinical trials, the availability of data from these trials and the timing of its regulatory submissions related to these 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, **the uncertainty regarding the COVID-19 pandemic including its impact on the timing of Aclaris' regulatory and research and development activities**, and other risks and uncertainties that are described in the Risk Factors section of Aclaris' Annual Report on Form 10-K for the year ended December 31, 2019, Aclaris' Quarterly Report on Form 10-Q for the quarter ended March 31, 2020 and other filings Aclaris makes with the U.S. Securities and Exchange Commission from time to time. These documents are available under the "SEC filings" 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.

Strategy: *Biotechnology company focused on developing small molecule therapeutics for immuno-inflammatory diseases*



LEADERSHIP

- Physician/Scientist founded and led
- World class ex-Pfizer kinase and ex-GSK immunology leadership
- Kinome experts skilled at developing kinase targeted medicines

KINect™ PLATFORM

Proprietary
Discovery Engine

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

INNOVATIVE PIPELINE

(investigational drug candidates)

ATI-450 – MK2i

- Oral anti-TNF α , anti-IL1, anti-IL6

ATI-1777-Topical Soft-JAK1/3i

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

ATI-2138 - ITK/TXK/JAK3i

- Oral dual inhibitor of T-cell and cytokine receptors

R&D Leadership Team

Experienced team with deep scientific and operational experience

David Gordon

Chief Medical Officer

Former SVP, R&D at GSK.
Led discovery and development teams in Immuno-Inflammation and Dermatology leading to multiple successful NDAs, including NUCALA® & BENLYSTA®

Joseph Monahan, PhD

*Exec. VP R&D
(Head of Discovery)*

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

Walter Smith

SVP, R&D

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

Jon Jacobsen, PhD

VP, Chemistry

Former Research Fellow and Director, Pfizer Chemistry
>100 publications and patents (15 total on kinases)
Project Lead for PFE JAK Program

Paul Changelian, PhD

VP, Biology

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

David R Anderson, PhD

Sr. Director, Discovery, Early Development







Former research project leader at Pfizer. Director of Chemistry at Mnemosyne, Luc, Cadent.
Inventor of 6 clinical candidates and author of 40 peer reviewed publications and patents

Gary DeCrescenzo

SVP, Pharm R&D

Former Exec. Director, Pfizer. Site Head for Medicinal & Structural Chemistry.
>100 patents.
Co-inventor of multiple drug candidates

Pipeline

Program	Indication(s)	Preclinical	Phase 1	Phase 2	Phase 3
ATI-450 MK2 Inhibitor <i>Oral</i>	Rheumatoid Arthritis				
	Additional Immuno-inflammatory Indication				
ATI-1777 JAK1/JAK3 Inhibitor <i>Soft Topical</i>	Atopic Dermatitis (moderate-to-severe)				
ATI-2138 ITK/TXK/JAK3 Inhibitor <i>Oral</i>	Psoriasis, Inflammatory Bowel Disease				
JAK1/JAK3 Inhibitor <i>Oral, gut-restricted</i>	Inflammatory Bowel Disease				
ITK/TXK/JAK3 Inhibitor <i>Oral, gut-restricted</i>	Inflammatory Bowel Disease				

The Kinase Opportunity

Creating New Medicines Targeting Previously Inaccessible Kinome Targets

Medically Important and Productive Target Class

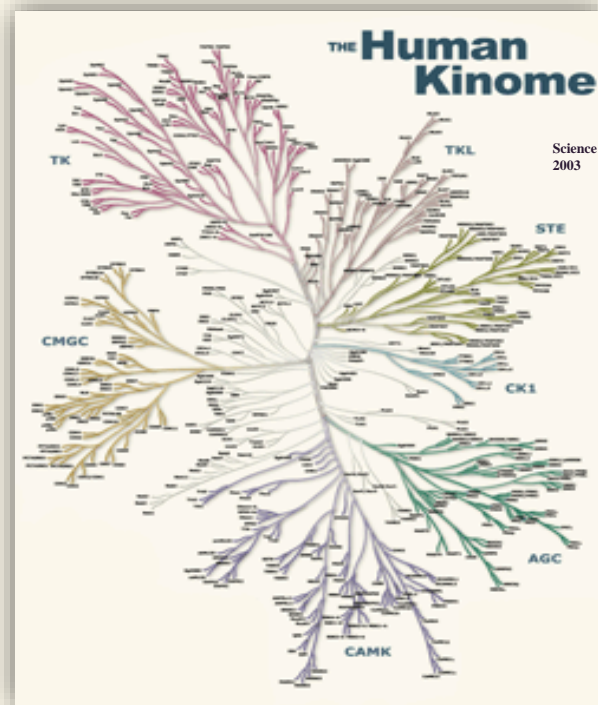


~36 Marketed Drugs

~\$48B*

Annual Sales of Kinase Drugs

Most Members of the Kinome Remain Unexplored



518 Members

>90% of the Human Kinome
remains undrugged

These drugs target less than 5% of the kinome

* Bologa C, et al. Unexplored opportunities in the druggable human genome. *Nat Rev Drug Discov.* 2018.

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Market Overview of Select Inflammatory Indications

	RA	Psoriasis	Ulcerative Colitis	Crohn's Disease	Atopic Dermatitis
	(moderate - severe)	(moderate - severe)	(moderate - severe)	(moderate - severe)	(moderate - severe)
2018E WW Sales¹	~\$25B	~\$15B	~\$5B	~\$11B	~\$1B
Estimated Peak Market (WW)²	~\$25-30B	~\$20-25B	~\$8-12B	~\$15B	~\$8-12B
Prevalent US Moderate/Severe Population³	~1,000K+	~1,000-1,300K	~400-500K	~350-450K	~300-700K
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.

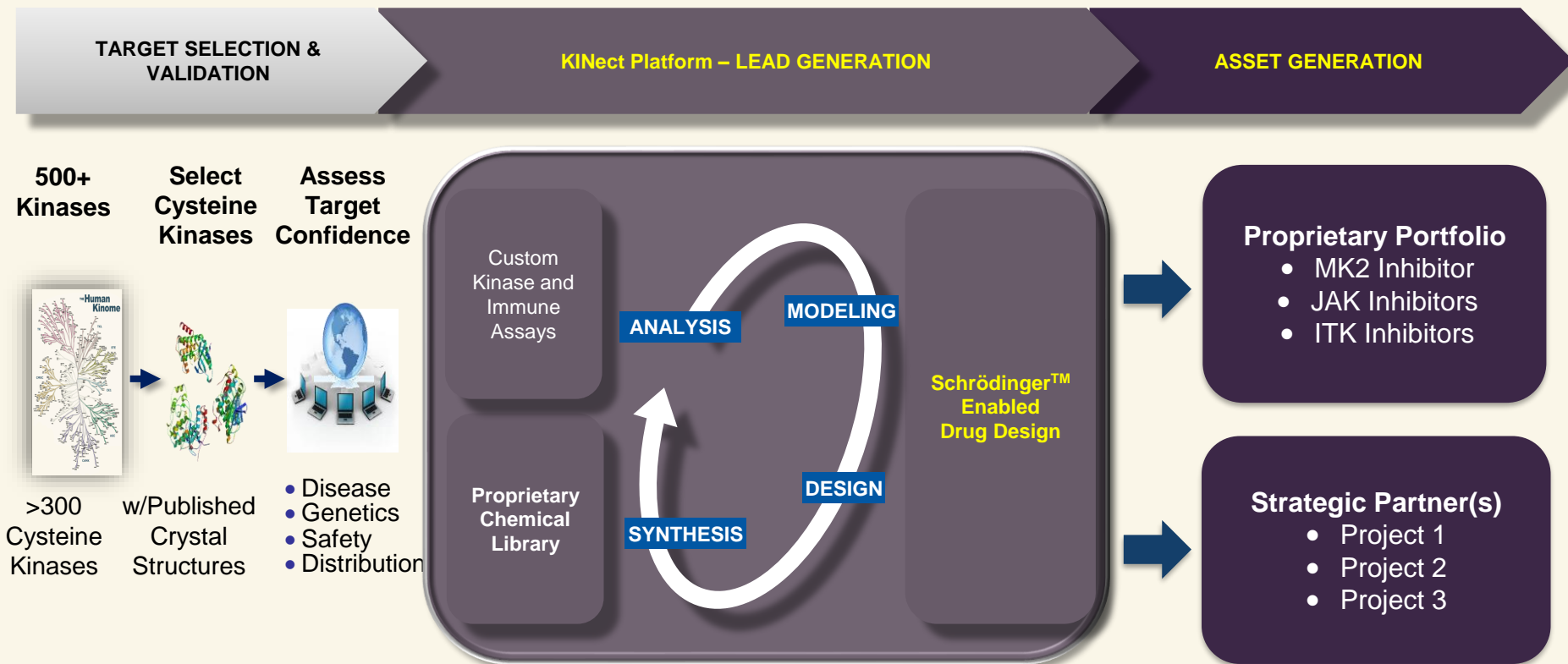
¹ Estimates of total sales per indication from EvaluatePharma.

² CS projections: based on US branded pricing.

³ Assumed peak treatable population with biologics/novel agents in the US: RA 350-400k / Psoriasis 300-350k / Ulcerative Colitis 225-275k / Crohn's 225-275k / Atopic Dermatitis 150-200k.

KINect Platform

Developing Kinase Drug Candidates Rapidly & Efficiently



- **Proprietary Library:** High affinity/selective drug scaffolds
- **Faster Path:** Decrease time to Lead Optimization by half or more
- **Multiple Approaches:** Design approach specific to each kinase

KINect™ Platform Demonstrated Success

Reversible and Covalent

MK2 Inhibitor

- Oral anti-TNF, anti-IL1, and anti-IL6
- Novel approach for a difficult to target kinase
- ATI-450 Phase 1 clinical trial data available

Tissue Restricted JAK and ITK Inhibitors

- Potential approaches to achieve efficacy with improved safety
- Skin specific: Soft, topical drug for the potential treatment of moderate-to-severe AD
- Gut-restricted inhibitor: for the potential treatment for inflammatory bowel disease

Covalent ITK Inhibitors

- ITK T cell kinase inhibitors for autoimmune diseases
- Oral and topical covalent drug candidates developed
- ATI-2138 (Oral): IND enabling work

Unique Substrate Selective Drug Design

Tailoring physico-chemical and potency properties

Covalent Inhibition: for difficult to target kinase

ATI-450: MK2 Inhibitor

(Investigational Drug Candidate)



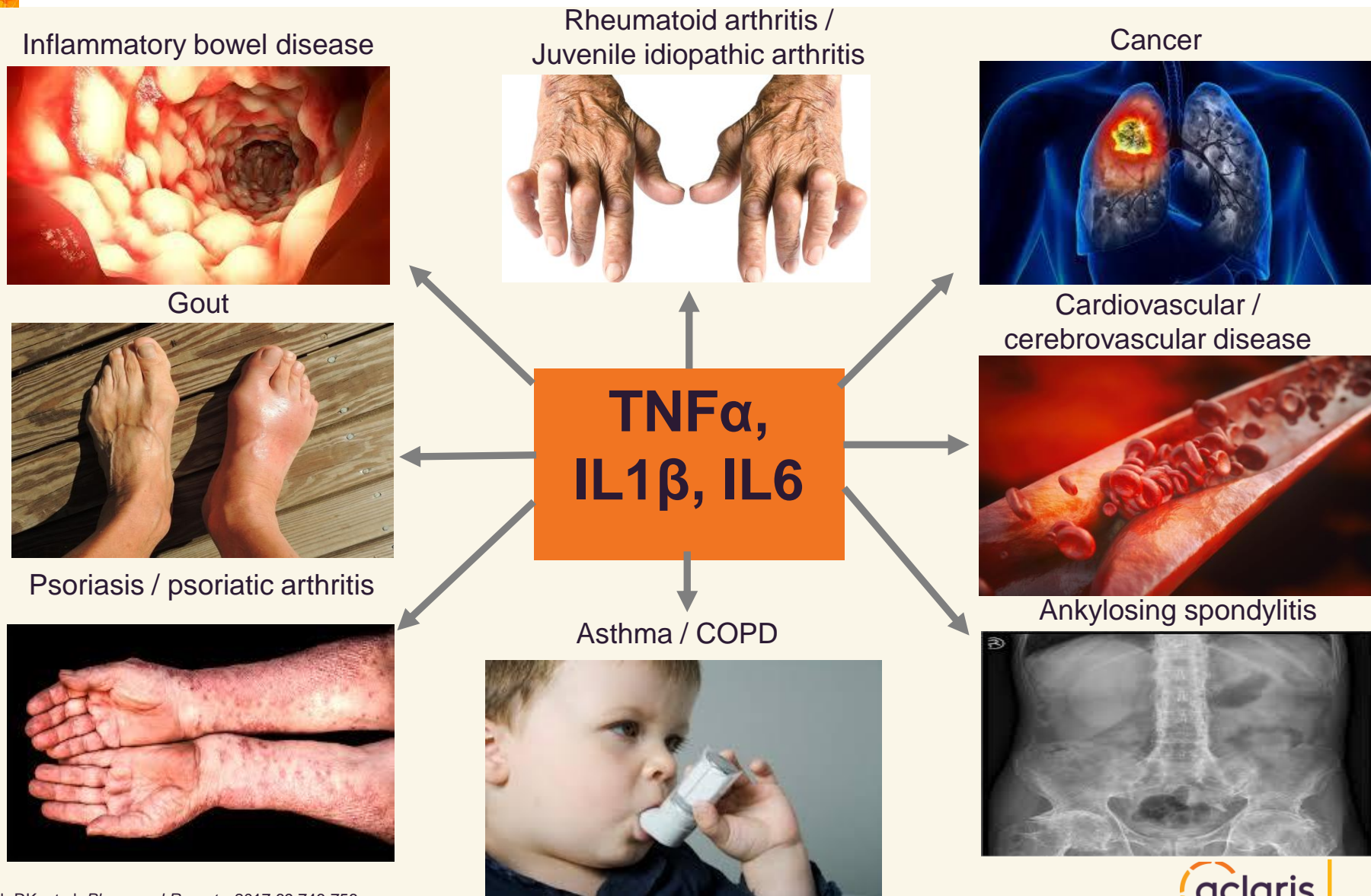
MK2 Inhibitor: Oral Small Molecule Inhibitor of TNF α , IL1, and IL6

- MK2* drives pro-inflammatory cytokine expression
- The effects of inhibiting MK2 mirror the effects of anti-inflammatory biologics¹
 - ✓ **anti-TNF α** : HUMIRA[®] (adalimumab), ENBREL[®] (etanercept), REMICADE[®] (infliximab)
 - ✓ **anti-IL1**: KINERET[®] (anakinra), ILARIS[®] (canakinumab), ARCALYST[®] (rilonacept)
 - ✓ **anti-IL6**: KEVZARA[®] (sarilumab), ACTEMRA[®] (tocilizumab)
- ATI-450: Small molecule MK2 inhibitor
 - ✓ Potential alternative to injectable, anti-cytokine biologics and JAK inhibitors for immuno-inflammatory diseases

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

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MK2-driven Cytokines are Central to Many Diseases

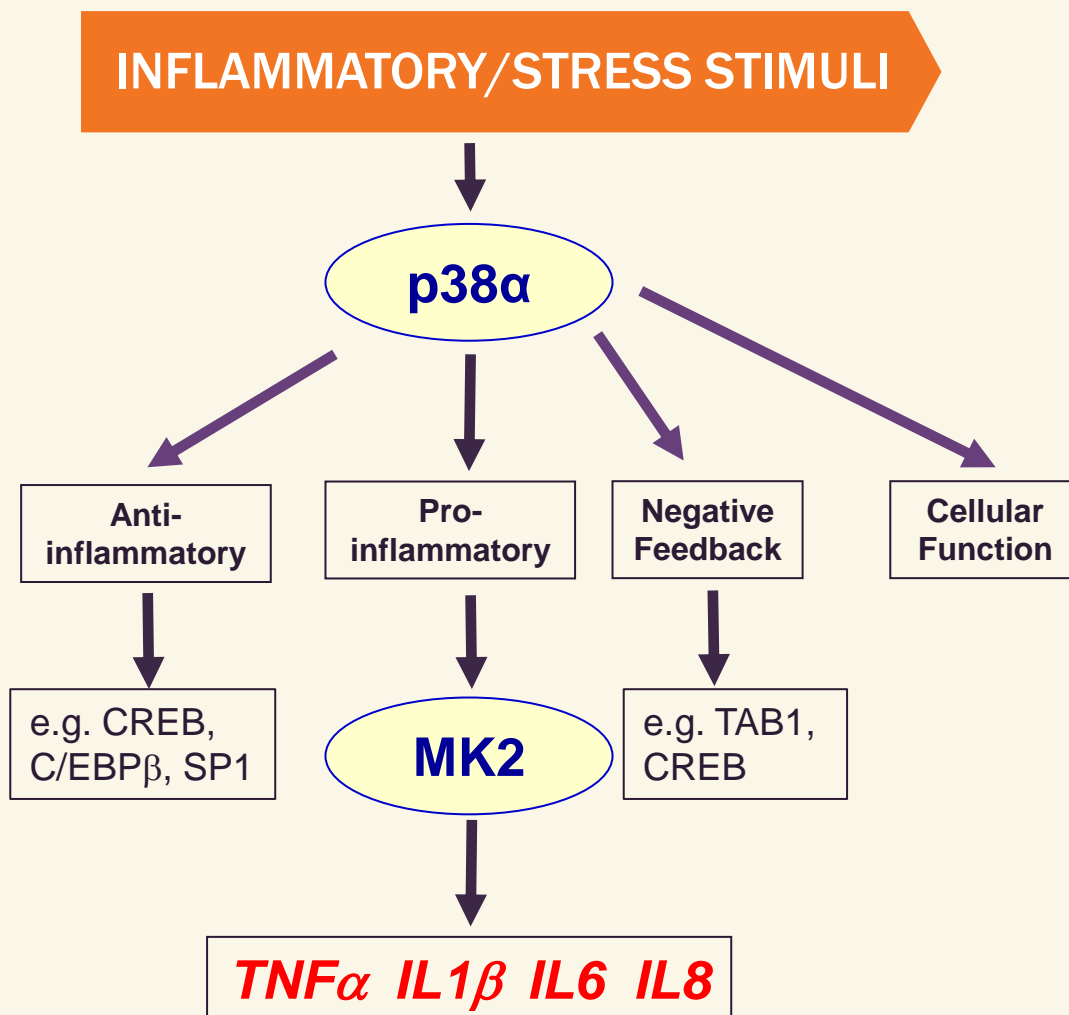


Evolution in Understanding of a Well-Known Path

The Path From p38 α to MK2

p38 α was initially targeted for suppressing TNF α and other pro-inflammatory cytokines

- Global p38 α inhibitors have exhibited toxicity and/or lack of sustained efficacy in RA and IBD
- p38 α phosphorylates over 60 substrates - yet MK2 drives the proinflammatory node of this pathway
- MK2 has been a high priority therapeutic target since 1999 but has proven very difficult to drug



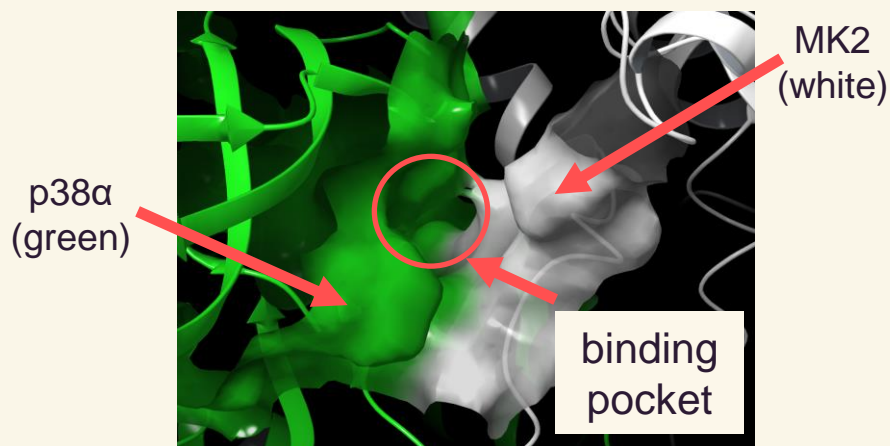
* Wang C, et al. *J Exp Med*. 2018;215(5):1315-1325.

* Cheung P, et al. *EMBO J*. 2003;22(21):5793-5805.

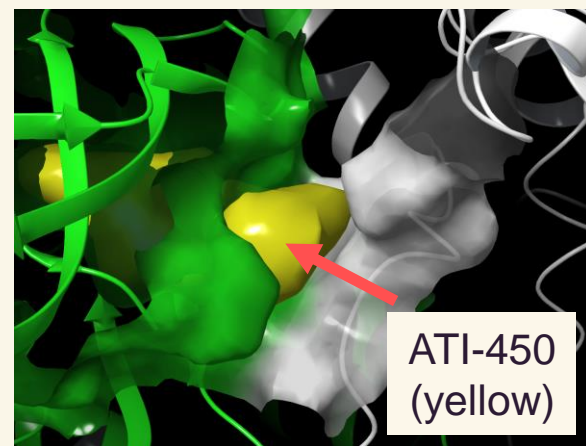
* Muniyappa H, et al. *Cell Signal*. 2008;20(4):675-683.

* Ma W, et al. *J Biol Chem*. 2001;276(17):13664-13674.

Novel mechanism: Capturing MK2 in an Inactive State



Crystal structure of the p38α/MK2 complex



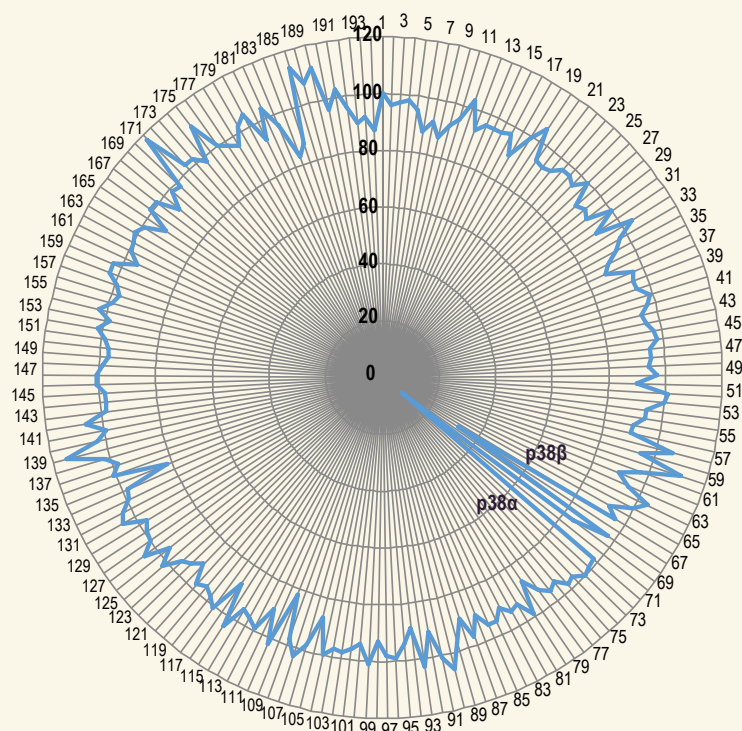
ATI-450 (yellow) docked in the pocket

- In the nucleus, inactive MK2 and p38α dock in a high affinity complex that exhibits a binding pocket formed by juxtaposed walls of both proteins
- ATI-450 binds to both walls of the pocket, stabilizing the complex and preventing MK2 activation

ATI-450 locks MK2 in a catalytically inactive state – a unique MOA

ATI-450 Selectivity

Human Kinome Selectivity¹



- ATI-450 (5μM) was tested vs 193 kinases
- >350-fold binding selectivity on all kinases in this panel except p38α and p38β

MK2 Pathway Selectivity

ATI-450 is highly selective for the p38/MK2 complex vs. other p38 substrates¹

Assay	Fold Selective
p38α/MK2	1
p38α/ATF2	700
p38α/PRAK	750

ATI-450 binds to the p38α/MK2 complex with higher affinity than either p38 or MK2 alone^{**}

Assay	Fold Selective
p38α/MK2	1
p38α/p38tide*	51
MK2/HSP27	>550

* Optimized p38 peptide substrate

** Data on file.

¹ Wang C, et al. *J Exp Med.* 2018;215(5):1315-1325.

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Animal Models Supporting the Development of ATI-450 in Immuno-Inflammatory Diseases

Therapeutic Area	Animal Model	Reference
Rheumatoid Arthritis / Psoriatic Arthritis	Rat streptococcal cell wall arthritis model <ul style="list-style-type: none"> • Protection against bone deterioration • Protection against lethality Inhibition of cellular IL1 β mRNA stability & translation	Wang C, et al. <i>J Exp Med.</i> 2018;215(5):1315-1325.
Inflammatory Bowel Disease	Adoptive transfer mouse model of colitis <ul style="list-style-type: none"> • Endoscopy scores show disease control • Decreased inflammatory infiltrate • Protected structural integrity of mucosa 	Strasser S, et al. <i>Integrative Biology.</i> 2019;11(7):301-314.
Cryopyrin-Associated Periodic Syndromes (CAPS)	Murine NOMID (severe form of CAPS) transgenic model Human CAPS PBMC* IL1 β modulation	Wang C, et al. <i>J Exp Med.</i> 2018;215(5):1315-1325.

* PBMC = Peripheral blood mononuclear cells

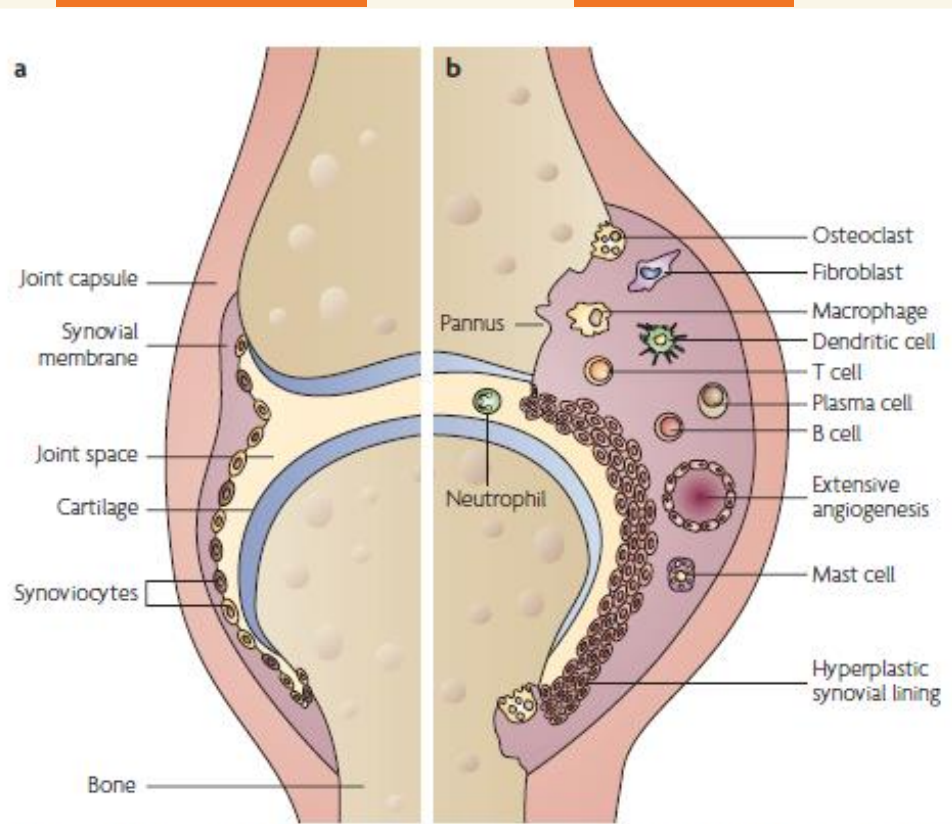
MK2 – Potential Effect in Rheumatoid Arthritis

ATI-450 regulates cells and cytokines involved in RA

MK2 is a key regulator of pathogenic signals in chronic immuno-inflammatory diseases

Normal Joint

RA Joint



Strand V, et al. *Nat Rev Drug Discov.* 2007;6(Jan 2007):75-92.

Cells

Monocyte/Macrophage

Osteoclast

Epithelial Cells

RA Synovial Fibroblast

Chondrocytes

Cytokines

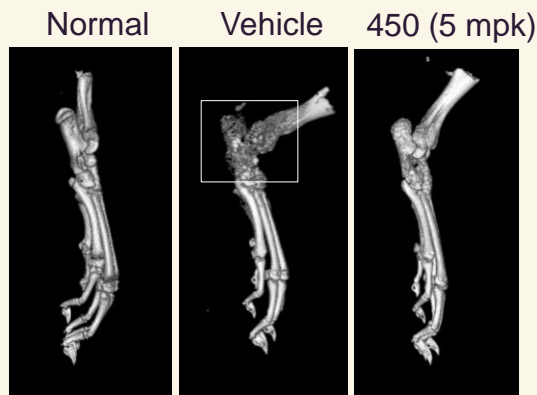
TNF α , IL1 β , IL1 α

IL6, IL8, IL18, RANKL

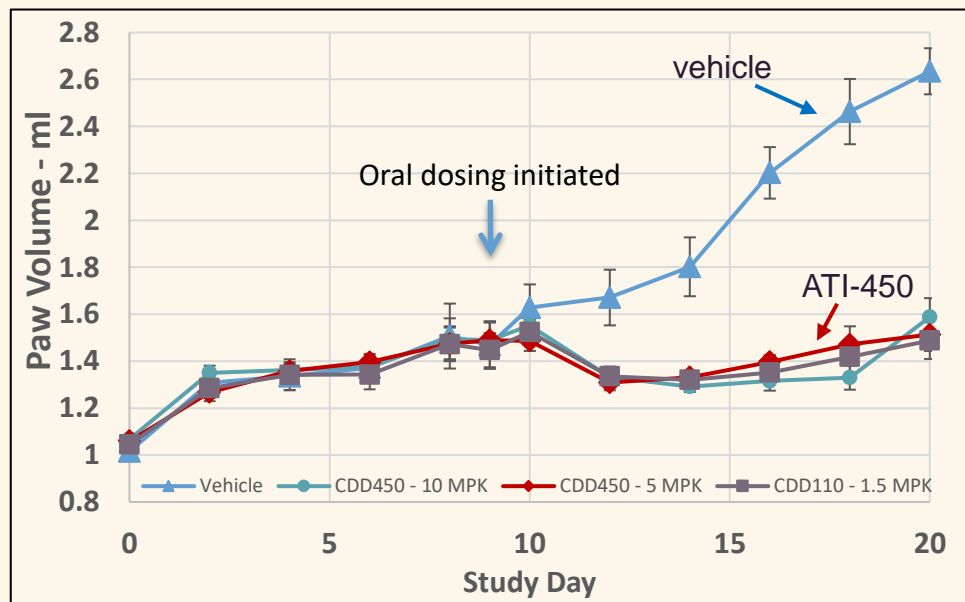
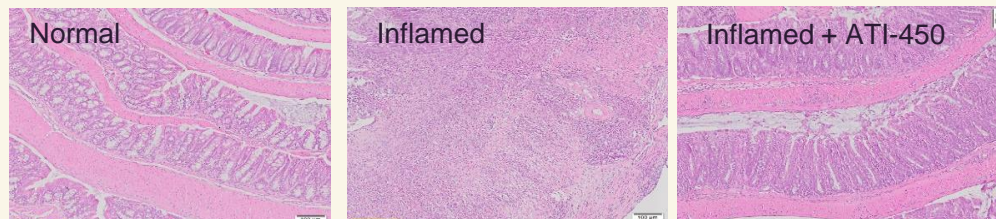
ATI-450: for bold items above data on file and Wang C, et al. *J Exp Med.* 2018;215 (5):1315-1325.

In vivo Preclinical Data of MK2 Pathway Inhibitor ATI-450

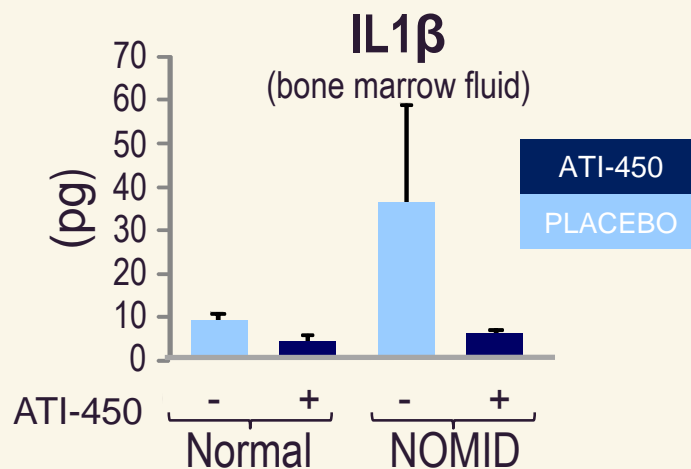
Joint Protection in Rat Arthritis Model¹



Blockade of Gut Inflammatory Infiltrate in Murine Adoptive Transfer Ulcerative Colitis Model²



Cytokine Modulation in Orphan Autoinflammatory Disease (CAPS)¹



¹ Wang C, et al. *J Exp Med*. 2018;215(5):1315-1325.

² Strasser S, et al. *Integrative Biology*. 2019;11(7):301-314.

Mouse Model: ATI-450 Inhibits RANKL-induced Osteoclastogenesis

Bone marrow derived macrophages (BMDM) from NOMID mice

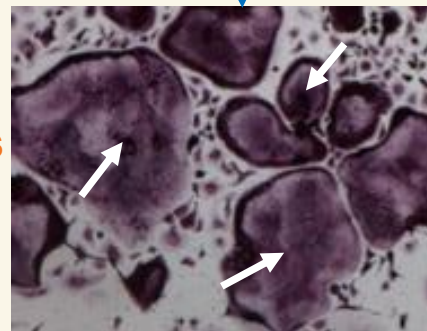
- In CAPS, osteoclastogenesis gives rise to low bone mass (osteopenia)
- (a) When bone marrow derived macrophages (BMDM) from NOMID mice are stimulated with RANKL (RANK ligand), they differentiate into osteoclasts
- (b) ATI-450 blocks this macrophage differentiation



NOMID BMDM



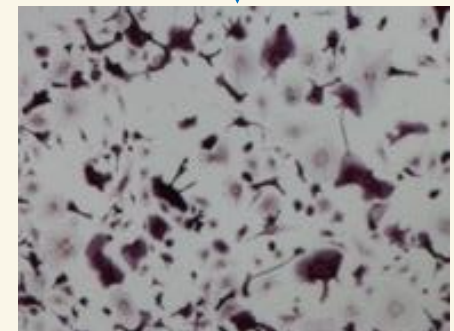
(a)



NOMID BMDM
Plus ATI-450



(b)

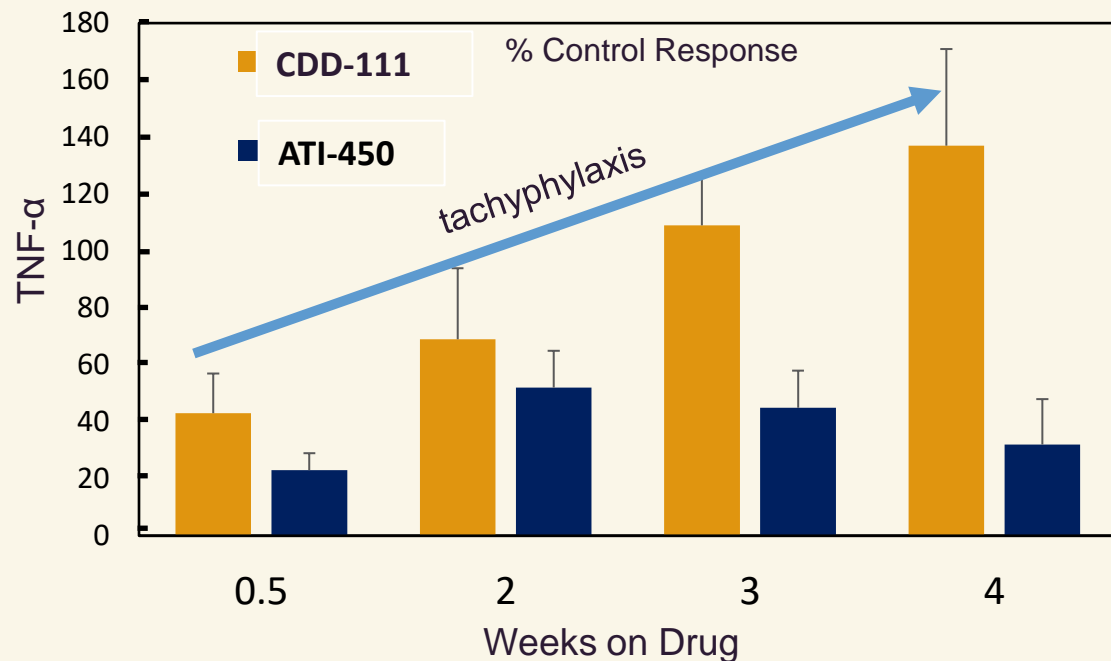


ATI-450 inhibits RANKL-stimulated macrophage differentiation into osteoclasts from NOMID mice

Mouse Model: LPS-Induced $\text{TNF}\alpha$ Production

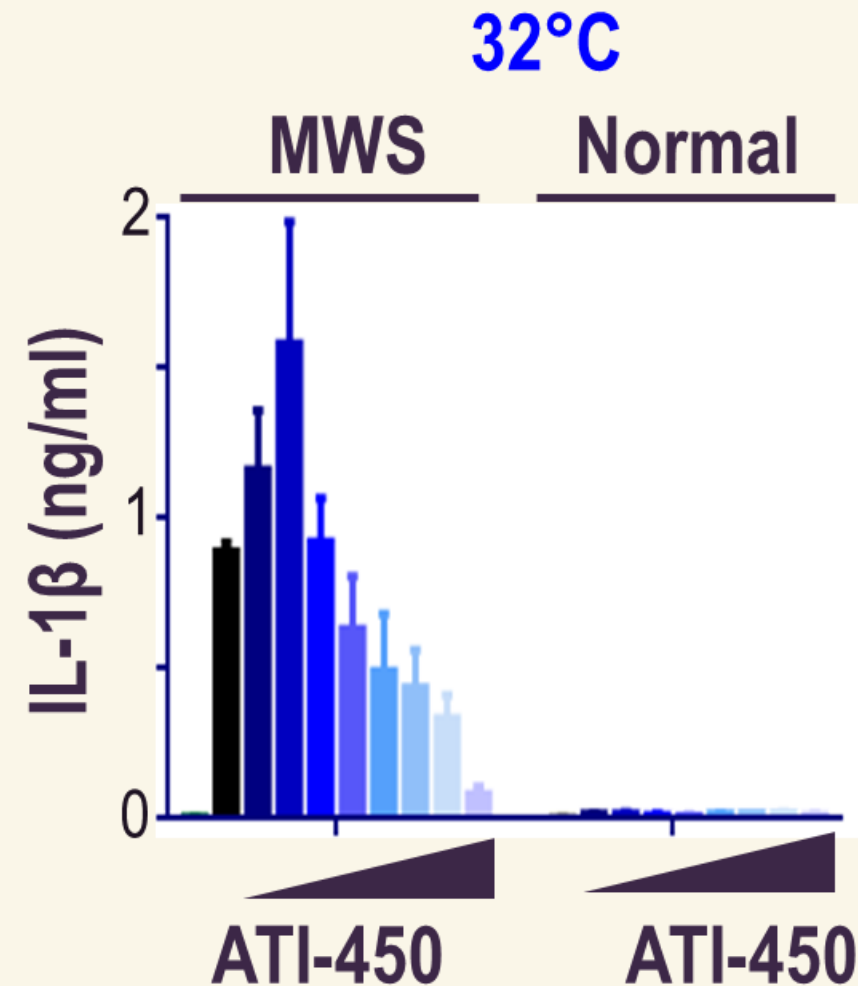
ATI-450 demonstrated durable response (no tachyphylaxis)

- Global investigational p38 inhibitor CDD-111 lost inhibition over time
- **MK2 inhibitor ATI-450 (investigational compound) demonstrated durable response (no tachyphylaxis)**



- CDD-111 and ATI-450 administered to mice in feed starting day 1 and continuing through day 28
- At the time point indicated, mice were LPS challenged and blood $\text{TNF}\alpha$ levels determined

Ex vivo Preclinical Data: ATI-450 Inhibits IL1 β Expression in PBMCs from a Patient with CAPS



- Peripheral blood mononuclear cells (PBMCs) were isolated from patients with CAPS and healthy controls.
- In patients with CAPS (Muckle Wells Syndrome; MWS), IL1 β expression is triggered by exposure to low temperatures.
- PBMCs from patients with CAPS spontaneously produced high amounts of IL1 β at 32°C but not at 37°C.
- ATI-450 blocks temperature stress induced IL1 β production.

ATI-450 Clinical Development

Phase 1 Single and Multiple Ascending Doses

- Safety, PK, Tolerability
- PD (inhibition of $\text{TNF}\alpha$, $\text{IL1}\beta$, IL6, IL8 & Hsp27)

Rheumatoid Arthritis Phase 2a Clinical Trial

- 12 wks: ATI-450 vs placebo
- Assess CRP dynamics
- Clinical Disease Activity/PD Biomarkers
- MRI: wrist synovitis
- Safety and tolerability

Demonstrate proof of
concept data

Autoinflammatory
Diseases

Inflammatory Bowel Disease

Psoriatic Arthritis

Hidradenitis Suppurativa

Psoriasis

Gout

Rheumatoid Arthritis

ATI-450-PKPD-101

Trial Design and Demographics

- Three-Part Study:
 - ✓ Part A: single ascending dose (SAD) plus food effect (n=32)
 - 4 cohorts: 10mg, 30mg, 50mg, 100mg (100mg repeated with high fat meal)
 - 8 subjects (6 active, 2 placebo). Single dose after overnight fast
 - ✓ Part B: multiple ascending dose (MAD) (n=30)
 - 3 cohorts: 10mg, 30mg, 50mg all BID for 7 days
 - 10 subjects (8 active, 2 placebo)
 - ✓ Part C: methotrexate (MTX) drug-drug interaction (DDI) (n=15)
 - 1 cohort: MTX day 1 and 8. ATI-450 on days 2-9
 - 15 subjects all dosed with active
- Demographics: (All dose groups, all parts)
 - ✓ Age: Mean 34 years
 - ✓ Gender: 44 female/33 male
 - ✓ Race: White-40, Black-32, Other-5

ATI-450-PKPD-101

Safety: ATI-450 Generally Well-Tolerated

Most Common Adverse Events (≥ 2 subjects in the trial)

SAD/MAD cohorts (blinded)

Preferred Term	ATI-450 n (%) (n=48)	Placebo n (%) (n=14)
Dizziness	6 (12.5)	0
Headache	10 (20.8)	2 (14.3)
Upper respiratory tract infection	3 (6.3)	1 (7.1)
Constipation	3 (6.3)	1 (7.1)
Nausea	2 (4.2)	1 (7.1)
Abdominal pain	2 (4.2)	0
Vomiting	0	2 (14.3)

DDI cohort (unblinded ATI-450 + MTX)

Preferred Term	ATI-450 n (%) (n=15)
Dizziness	7 (46.7)
Headache	1 (6.7)
Upper respiratory tract infection	1 (6.7)
Constipation	0
Nausea	0
Abdominal pain	0
Vomiting	0

- No serious adverse events or adverse events that led to discontinuation of study medication
- All adverse events were mild in severity and did not interfere with everyday activities
- A trend of a decrease in absolute neutrophil count was observed
 - ✓ No correlation with clinical sequelae
 - ✓ This effect is consistent with the pharmacodynamic profile of certain anti-TNF therapies¹

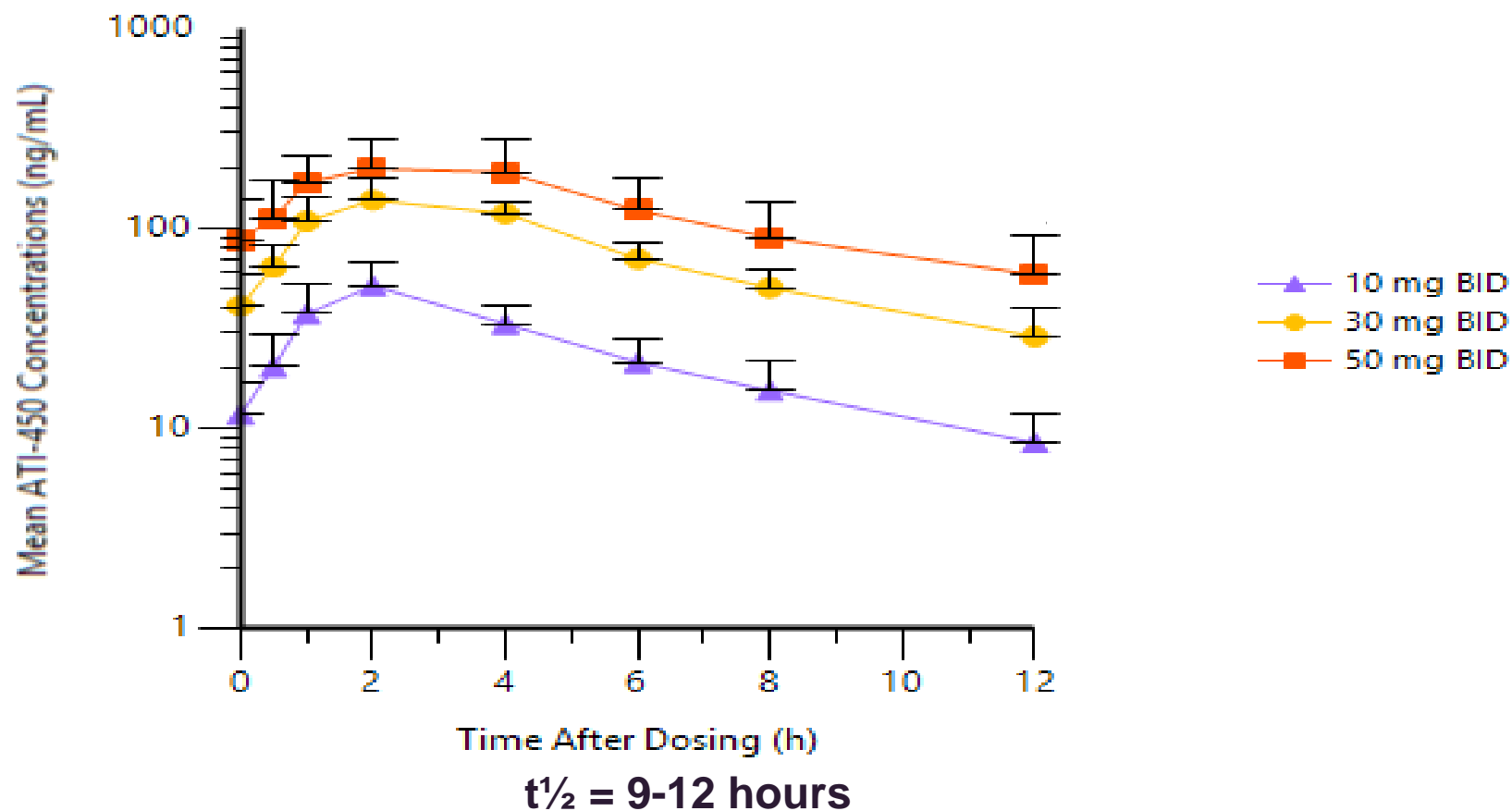
¹ Dillingh M, et al. *Front. Immunol.* 2016;7(508):1-9.

* Data on file.

ATI-450-PKPD-101

MAD Pharmacokinetics: Dose Proportional PK

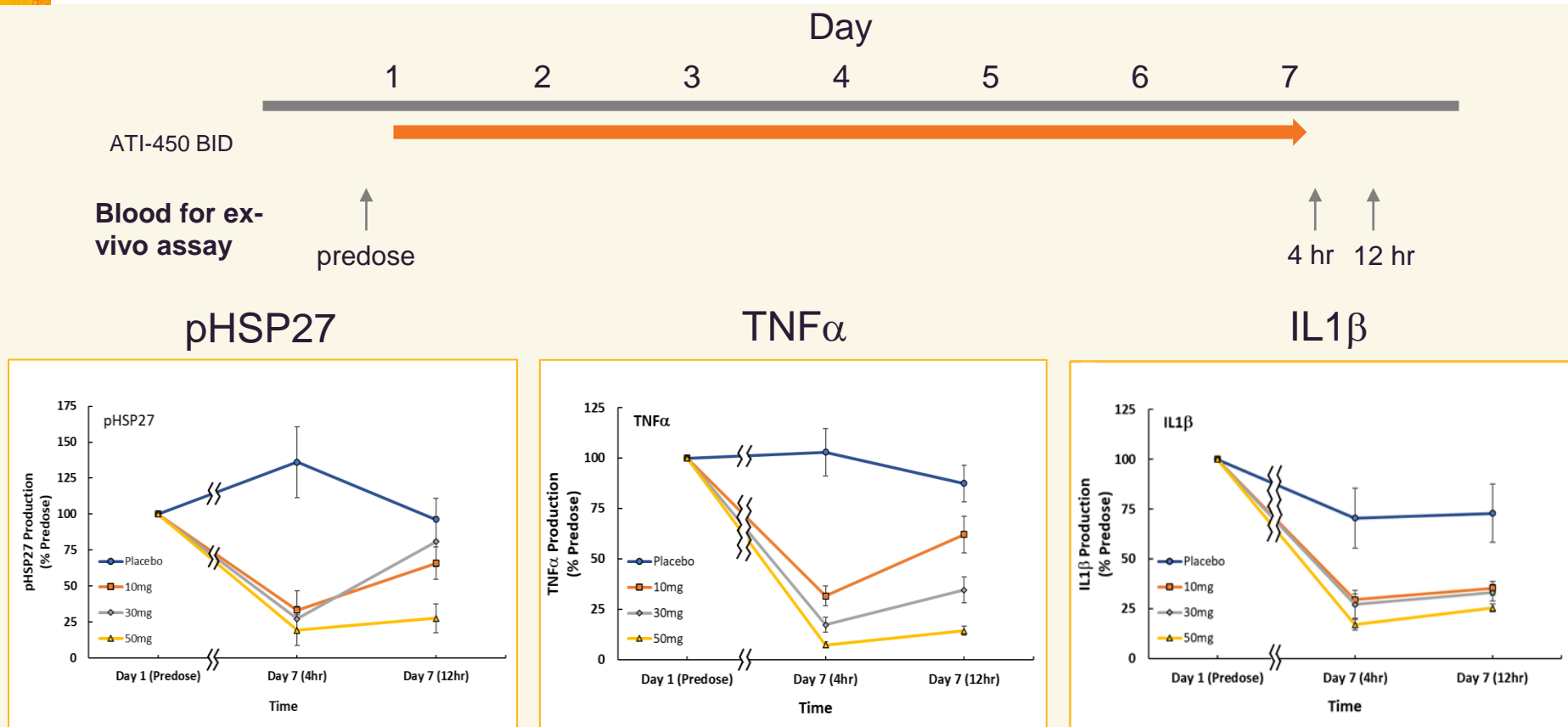
Mean (SD) plasma concentration-time profiles of ATI-450: Day 7



* Data on file

ATI-450-PKPD-101: Day 7 MAD PD Marker Time Dependence

Target Biomarker pHSP27 and Cytokines $TNF\alpha$ and $IL1\beta$

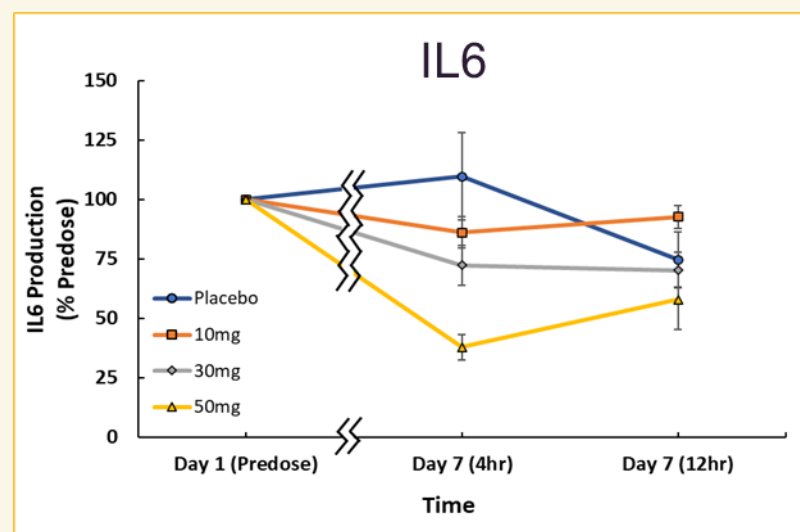
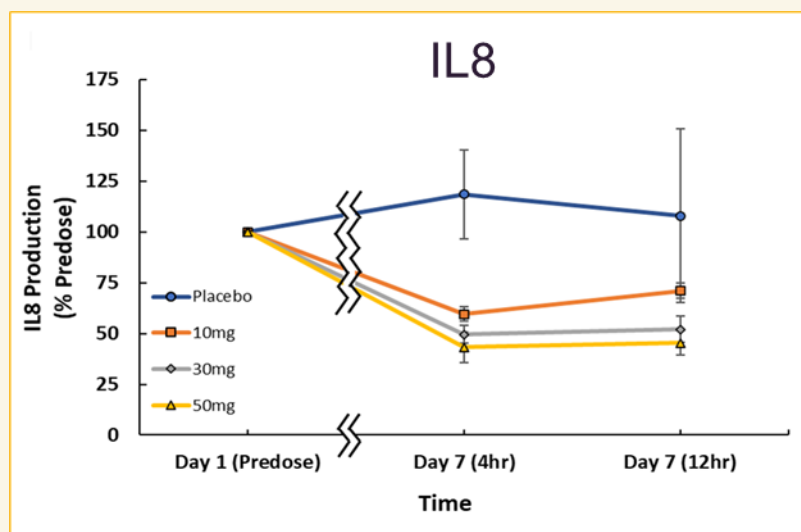
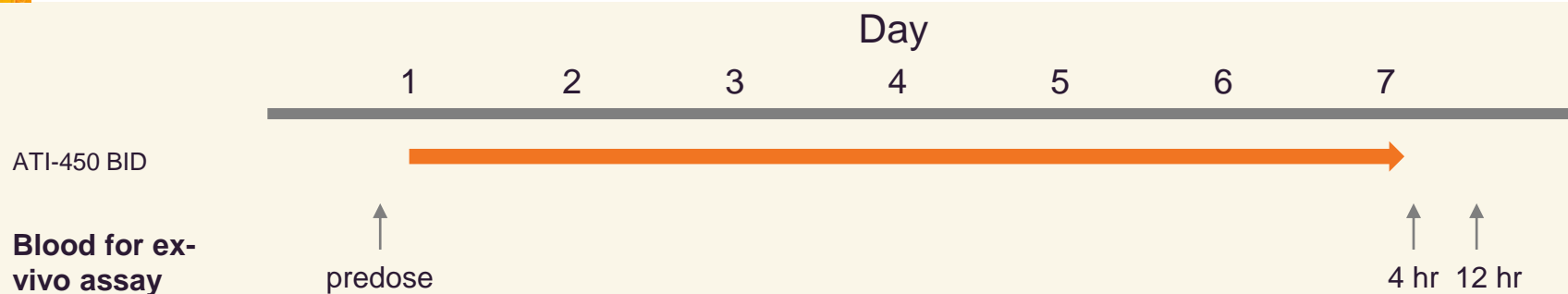


- ATI-450 dosed orally BID for 7 days in healthy subjects at doses of 10mg, 30mg and 50mg
- Day 1 (predose) is from blood taken on day 1 just prior to the first dose of ATI-450
- Samples ex vivo stimulated with LPS
- Data expressed as mean +/- SEM

* Data on file

ATI-450-PKPD-101: Day 7 MAD PD Biomarker Time Dependence

Cytokines IL6 and IL8



- ATI-450 dosed orally BID for 7 days in healthy subjects at doses of 10mg, 30mg and 50mg
- Day 1 (pre-dose) is from blood taken on day 1 just prior to the first dose of ATI-450
- Samples ex vivo stimulated with LPS
- Data expressed as mean +/- SEM

* Data on file

ATI-450-PKPD-101

Multiples of Cytokine IC₈₀ Across Dosing Interval

The MAD 50mg BID cohort achieved systemic drug concentrations in excess of IC₈₀ for pHSP27, TNF α , IL1 β and IL8 at C_{max} (3.5-6.0X) and C_{trough} (1.4-2.4X).

Biomarker	*IC ₈₀ ng/ml	**C _{trough} Multiple of IC ₈₀	**C _{max} Multiple of IC ₈₀
pHSP27	36.7	2.4x	6.0x
TNF α	62.6	1.4x	3.5x
IL1 β	40.8	2.2x	5.4x
IL6	747.8	0.1x	0.3x
IL8	38.8	2.3x	5.6x

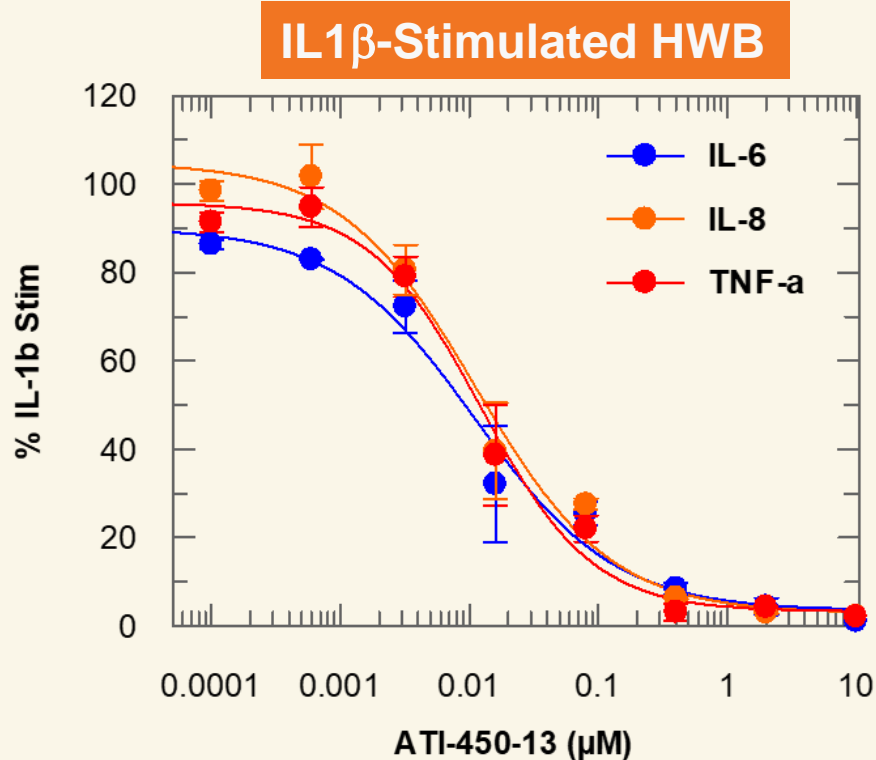
*IC₈₀ values generated with all SAD/MAD exposure data using the E_{max} model in WinNonlin

** 50 mg BID MAD Cohort

50 mg BID C_{trough} = 87.9 ng/ml

50 mg BID C_{max} = 215 ng/ml

In Vitro Model: ATI-450 Inhibits IL1 β -Stimulated Cytokines in Human Whole Blood



Cytokine	IC ₈₀ (ng/ml)
TNF α	31 \pm 6
IL6	41 \pm 20
IL8	40 \pm 12

ATI-450 was added to freshly isolated human whole blood for 1 hr and stimulated with IL1 β (10 ng/ml) for 5 hrs. Cytokines were measured by Meso Scale Discovery technology.

MK2 inhibitor ATI-450 Summary

- Discovered a novel approach to drug the target
- Potential alternative for diseases treated by biologics and JAK inhibitors
 - ✓ Robust efficacy in a range of inflammation and mouse cancer models^{1,2}
- Phase 1 SAD/MAD Data*
 - ✓ Generally well-tolerated at all doses
 - ✓ Dose response noted
 - ✓ Potent target suppression: ATI-450 dosed at 50 mg BID drove plasma levels 1.4-2.4x greater than those required to hit an IC80 for 4 key biomarkers
- Phase 2a clinical trial in Rheumatoid Arthritis underway

* Data on file

1 Murali B, et al. *Cancer Res.* 2018;78(19):1-13.

2 Wang C, et al. *J Exp Med.* 2018;215(5):1315-1325.

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ATI-1777 (Topical Soft-JAK Inhibitor)

(Investigational Drug Candidate)



Atopic Dermatitis Opportunity

- Atopic dermatitis (AD) is a chronic, pruritic inflammatory skin condition¹
 - ✓ The prevalence rate for AD in the US is 10-12% in children and 0.9% in adults²
 - ✓ Market projected to be \$8-12 billion at peak (moderate-to-severe AD)³
 - ✓ Systemic and topical JAK inhibition has demonstrated promising results in AD clinical trials⁴

Approach	Status
<ul style="list-style-type: none">• Comparable efficacy to other topical JAKs but “soft” drug to minimize the potential for systemic immunosuppression• JAK1/3 selective to minimize JAK2 inhibition toxicity• Deliver in a patient-friendly formulation• Patients with moderate-to-severe AD	<ul style="list-style-type: none">• IND mid year• Next key milestone: First In Human - 2H2020• Plan to study in patients with moderate-to-severe AD

1 <https://emedicine.medscape.com/article/1049085-overview>. Last accessed 5-26-20.

2 <https://emedicine.medscape.com/article/1049085-overview#a8>. Last accessed 5-26-20.

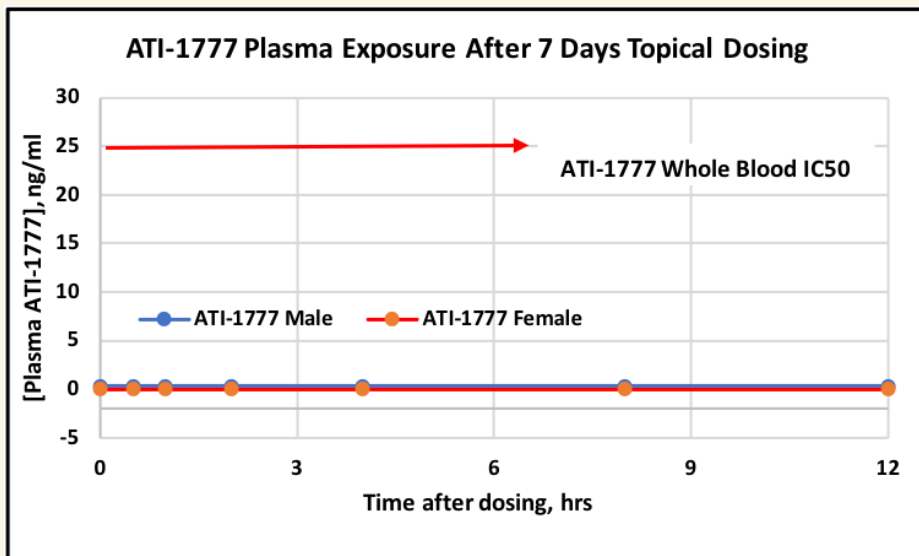
3 Auster M, et al. Something Big Is Getting Bigger [research note]. *Credit Suisse Equity Research*; 2019.

4 Shreberk-Hassidim R, et al. *J Am Acad Dermatol*. 2017;Apr;76(4):745-753.

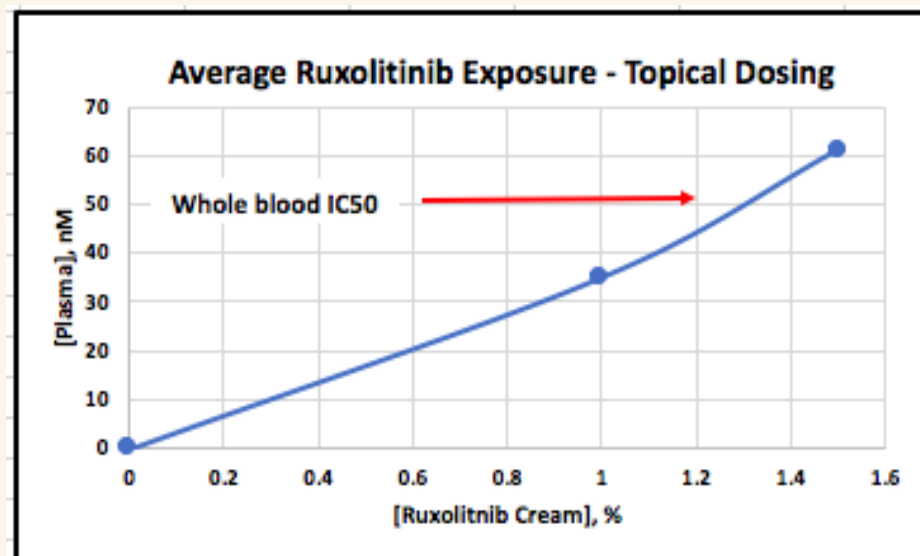
Minipig Model: ATI-1777 Nonclinical Safety Program TK Data

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

- No adverse effects noted (10% body surface area, QD)
- Bleeds at 0.5, 1, 2, 4, 8, 12, and 24 hours post-application: Days 1 and 6
- All plasma samples were below limit of quantification (<0.50 ng/mL) – well below cellular IC₅₀



MINIPIG¹



HUMAN^{2,3}

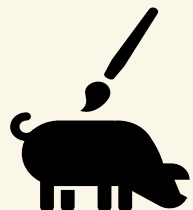
¹ Data on file.

² Chen X, et al. *Clin Pharmacol Drug Dev.* 2013;3(1):34–42.

³ Punwani N, et al. *Br J Dermatol.* 2015;173:989–997.

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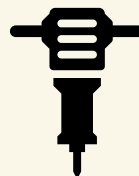
Porcine Model: ATI-1777 Blocks IL15 Induced CCL8 mRNA in Skin



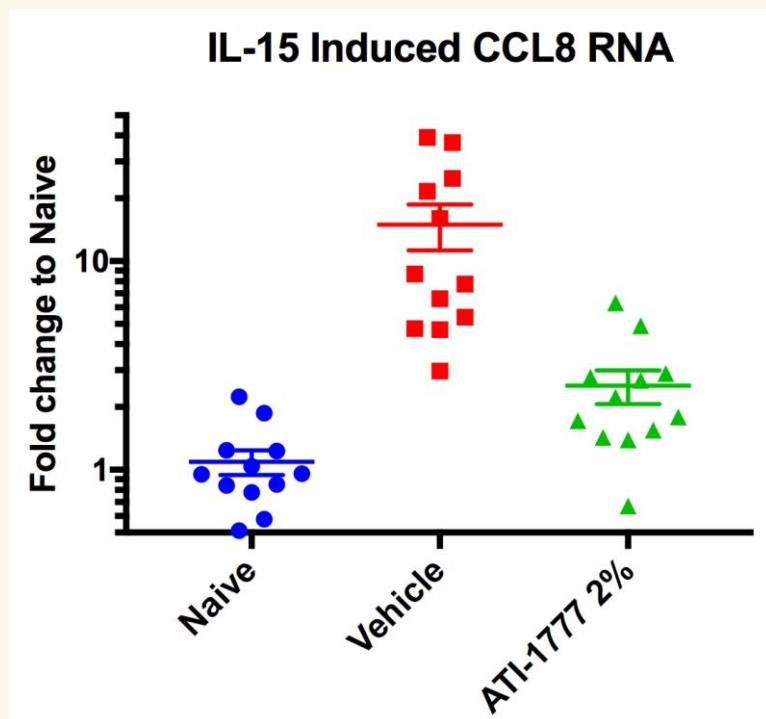
Apply
formulation to
back of pig,
wait 1 hr



Intra-dermal
Injection of
porcine IL15,
wait 3 hr



Harvest 6 mm
biopsy,
prepare RNA,
measure CCL8
by qPCR



- Single application of 2% ATI-1777 development formulation significantly inhibits IL15 (JAK1/3) induced gene induction (CCL8).

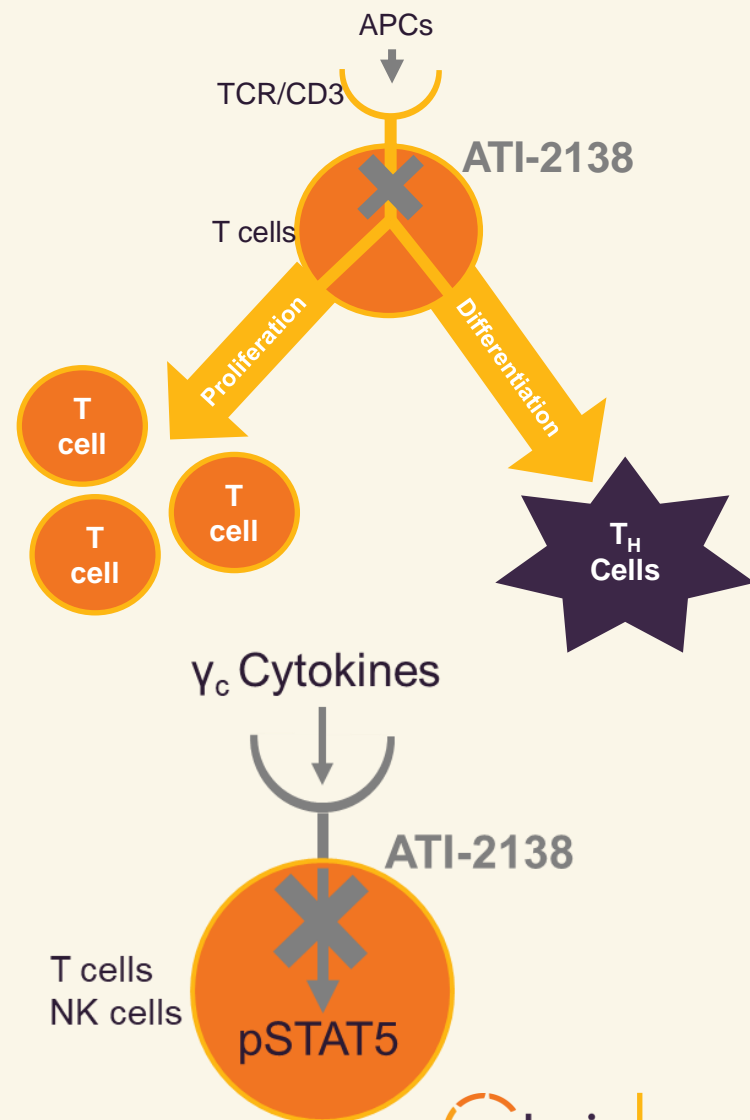
ATI-2138 (ITK/TXK/JAK3 Inhibitor)

(Investigational Drug Candidate)

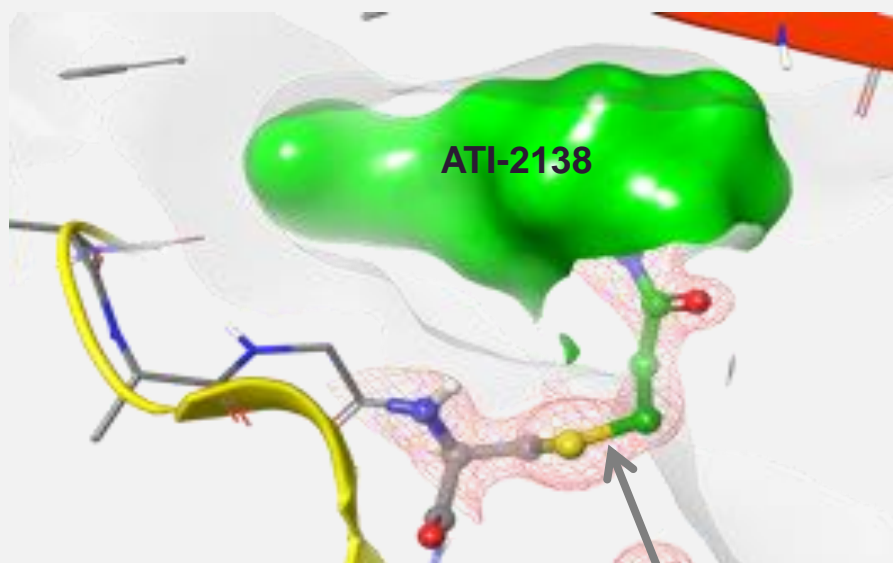


ATI-2138: Covalent ITK/TXK/JAK3 (ITJ) Inhibitor

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



ATI-2138 is a Potent Covalent Inhibitor



Covalent bond between
ITK^{Cys} and ATI-2138

**Co-Crystal Structure of ATI-2138/ITK -
shows ATI-2138 covalent binding to ITK**

Cellular Inhibition of JAK and ITK/TXK

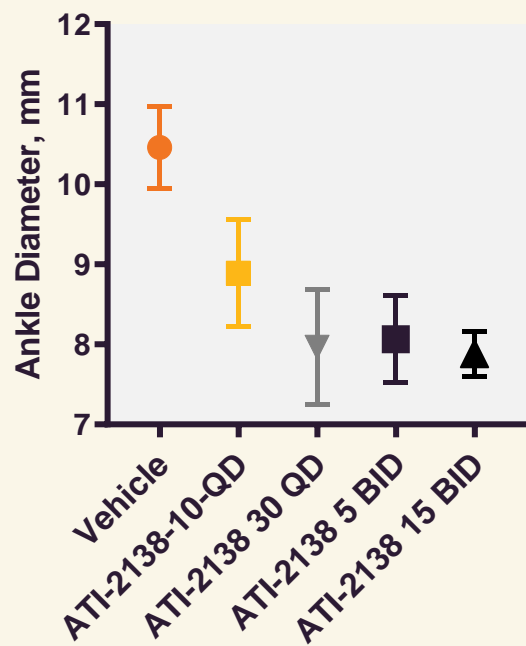
Assay Description	ATI-2138 IC ₅₀ (nM)	Assay
ITK/TXK activity	7	Jurkat pPLCγ-1
JAK1/3 activity	20	PBMC pSTAT-5
Both ITK/TXK and JAK3	13	HWB αCD3/IL15 IFNγ
BTK activity	52	Ramos pPLCγ-2

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

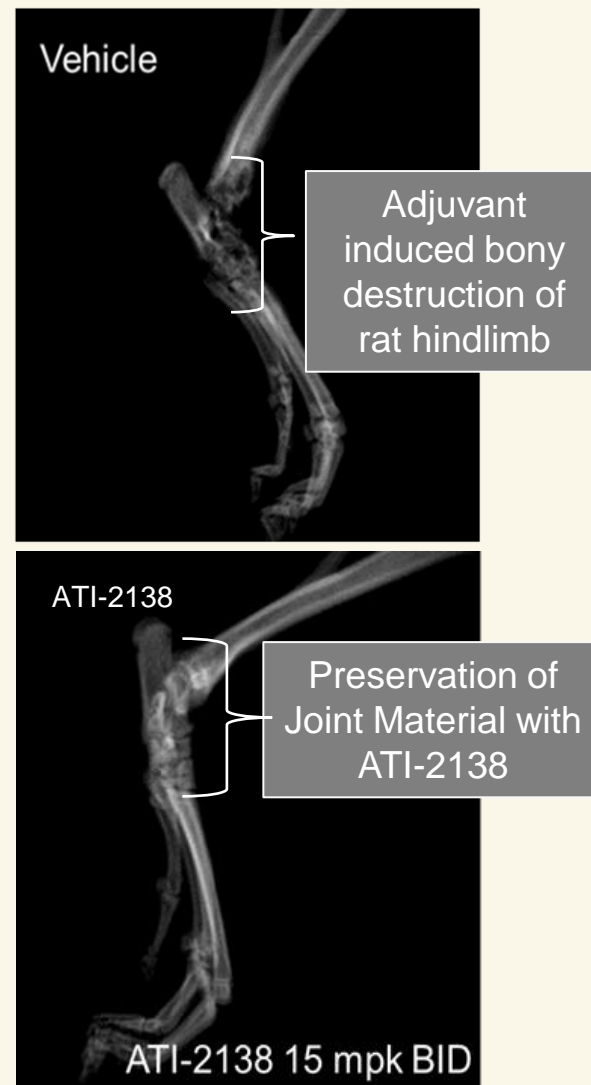
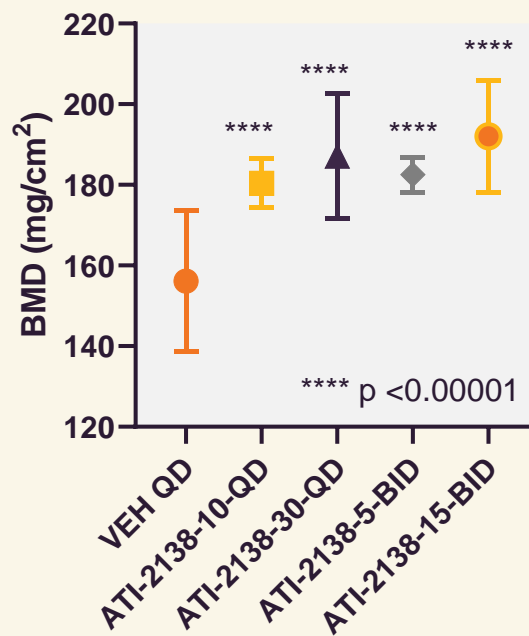
Rat Adjuvant Induced Arthritis (AIA) Model: ATI-2138 Reduced Inflammation and Protected Bone



Day 23 ankle diameter

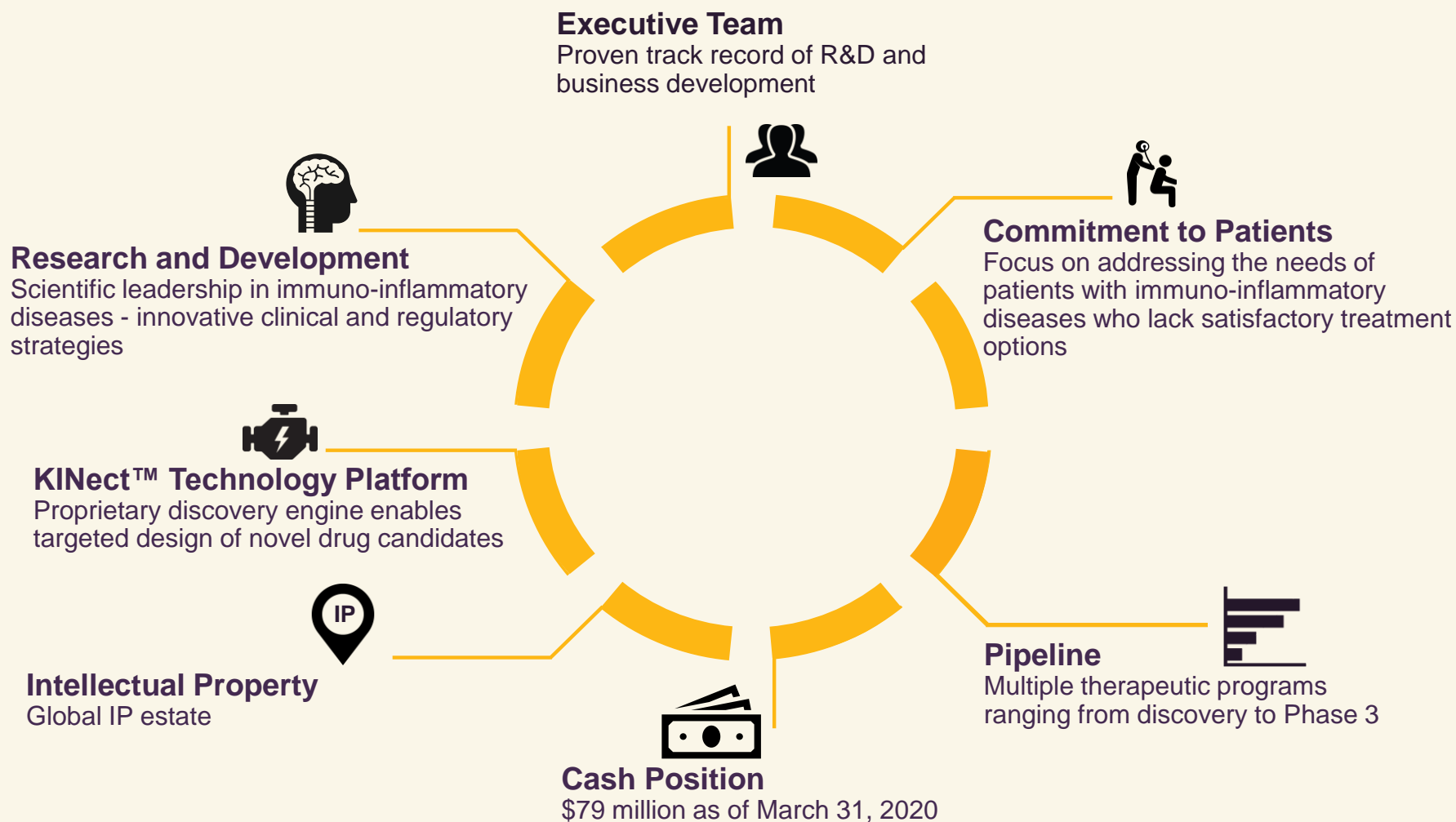


ATI-2138 bone mineral density in rat AIA study



ATI-2138 reduced inflammation and bone mineral density loss

Biopharmaceutical Company



Catalysts

Milestone	2020				2021	
	1Q	2Q	3Q	4Q	1Q	2Q
ATI-450 (MK2 Inhibitor)						
Phase 1 Data (SAD/MAD)	✓					
Initiate Phase 2a Trial in Rheumatoid Arthritis	✓					
ATI-1777 (Topical Soft-JAK Inhibitor)						
Submit IND						
Initiate Phase 1/2 Trial						
ATI-2138 (ITK/TXK/JAK3 Inhibitor)						
Submit IND						
Initiate Phase 1 Trial						

EMPOWERING PATIENTS THROUGH
KINOME INNOVATION

THANK YOU

