Aclaris Therapeutics R&D and Investor Day
October 4, 2017
Immuno-Dermatology Pipeline Review

ACLARIS THERAPEUTICS

Confluence Introduction

October 04, 2017

Confluence
DISCOVERY TECHNOLOGIES
A Wholly Owned Subsidiary of Aclaris Therapeutics, Inc.

CHARTING NEW TERRITORIES IN KINASE DRUG DISCOVERY

Quality Research Partners from IDEA to IND

Forward Looking Statement

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 the research and development, and potential attributes, of the drug candidates of Confluence Discovery Technologies, Inc. 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, 2016, Aclaris' Quarterly Report in Form 10-Q for the quarter ended June 30, 2017, and other filings Aclaris makes with the U.S. Securities and Exchange Commission from time to time. These documents are available under the "Financial Information" 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 release, and Aclaris assumes no obligation to, and does not intend to, update any forward-looking statements, whether as a result of new information, future events or otherwise

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 THERAPEUTICS

Confluence Corporate Highlights

- History of discovering novel innovative therapies for autoimmune disease and chronic inflammation
- Proven R&D leaders and world-class kinase experts
- Potentially best-in-class MK2 Pathway Inhibitor to block inflammatory cytokines
- Multiple product opportunities from the JAK and Tec kinase families for autoimmune disease
- Fully integrated research team from medicinal chemistry → pharmacology → drug development

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Confluence Leadership - Ex-Pfizer “Kinase Experts”

Walter Smith *CEO*	**Joseph Monahan, PhD** *CSO/Founder*	**Jon Jacobsen, PhD** *Chemistry Director*	**Paul Changelian, PhD** *Biology Director*
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	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®

Program Initiation → ***Hit*** → ***Lead*** → ***Candidate*** → ***IND***

BIOLOGY and COMPOUND PROFILING
- Enzyme/Cellular assay development and screening
- Immunology models
- *In vivo* efficacy studies
- *In vitro* ADME
- *In vitro /In vivo* Metabolite profiling
- *In vivo* DMPK
- *In vivo* toxicology

CHEMISTRY
- Structure based drug design
- Medicinal Chemistry
- API synthesis
- Process Development
- Pre-Clinical cGMP API production
- CMC generation
- Patent filing

PRE-CLINICAL IND ENABLING STUDIES (GLP)
- GLP Analytics
- Drug-Drug Interaction
- Genetic toxicology
- Safety pharmacology
- Definitive PK
- General toxicology
- Biomarker development

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Confluence Life Sciences

Assets	• JAK inhibitors - oral and topical - (next generation) • ITK inhibitors - oral and topical - (“anti-IL-17”) • MK-2 inhibitor - oral - (“anti-TNF” and “anti-IL-1β”)
Platform	• KINect™ platform – drug discovery engine • Proprietary compound library and computational chemistry capability • Medicinal chemistry, disease biology, immunology, pharmacology and preclinical development expertise
People	• Co-inventors of tofacitinib and former leaders of Pfizer kinase program (including JAK inhibitors) • Kinome experts - chemists and biologists; combined 300+ years of drug discovery experience • Significant experience in small molecule drug discovery through Phase II

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Confluence Assets

MK-2 Pathway Inhibitor ATI-450 "Oral Anti-TNF"	• Psoriasis / Psoriatic Arthritis, RA, CAPS*, Chronic Inflammation • Highly potent and designed to escape tachyphylaxis associated with global p38 kinase inhibitors
JAK Inhibitors	• Alopecia Areata, Vitiligo, AGA**, Inflammatory Disorders • Highly selective, covalent and non-covalent. Oral and soft topical formulation
ITK Inhibitors "Oral Anti-IL17"	• Atopic Dermatitis, Psoriasis • Oral and soft topical formulation
Early Discovery Portfolio	• Leverage mechanisms in play to maximize opportunities • Utilize KINect™ platform for exciting new kinase targets

*CAPS: Cryopyrin-Associated Periodic Syndromes
**AGA: Androgenetic Alopecia

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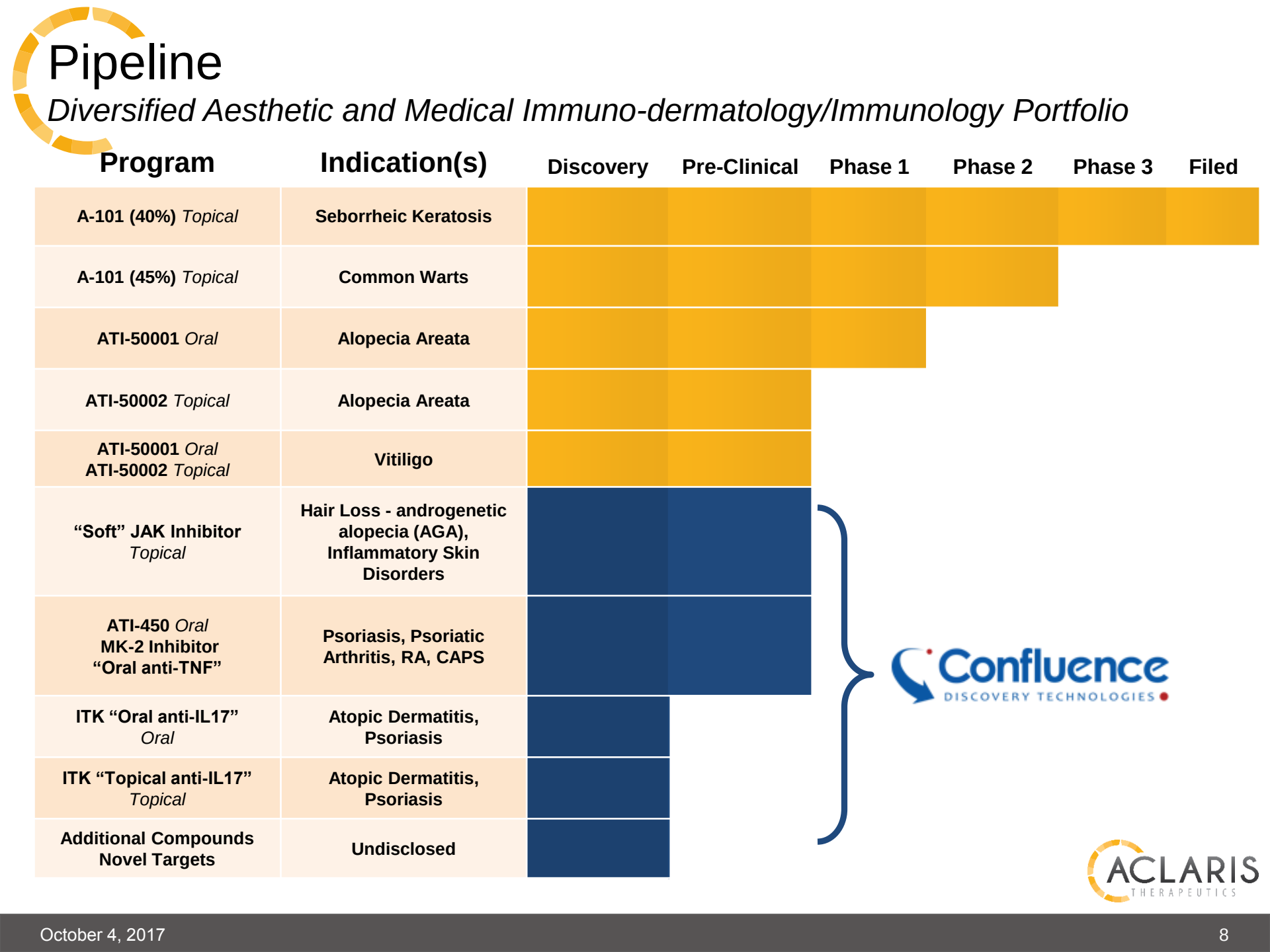
Pipeline

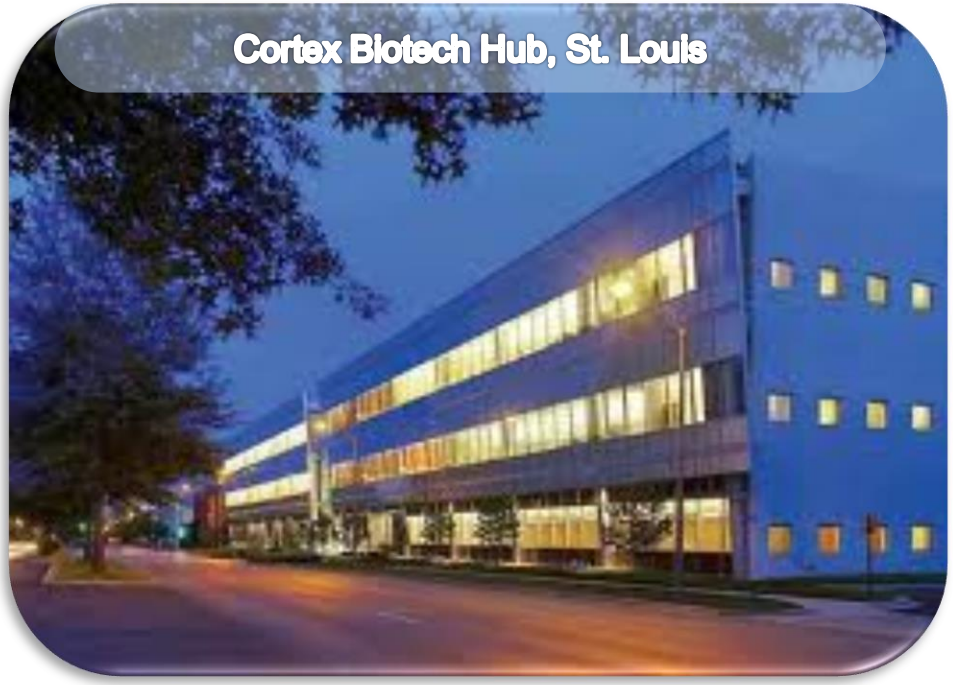
Diversified Aesthetic and Medical Immuno-dermatology/Immunology Portfolio

Program	Indication(s)
A-101 (40%) *Topical*	**Seborrheic Keratosis**
A-101 (45%) *Topical*	**Common Warts**
ATI-50001 *Oral*	**Alopecia Areata**
ATI-50002 *Topical*	**Alopecia Areata**
ATI-50001 *Oral* **ATI-50002** *Topical*	**Vitiligo**
"Soft" JAK Inhibitor *Topical*	**Hair Loss - androgenetic alopecia (AGA), Inflammatory Skin Disorders**
ATI-450 *Oral* **MK-2 Inhibitor** **"Oral anti-TNF"**	**Psoriasis, Psoriatic Arthritis, RA, CAPS**
ITK "Oral anti-IL17" *Oral*	**Atopic Dermatitis, Psoriasis**
ITK "Topical anti-IL17" *Topical*	**Atopic Dermatitis, Psoriasis**
Additional Compounds Novel Targets	**Undisclosed**



Confluence Discovery Technologies

- Contract Research Partner
- Custom pharma R&D
  - Biochemistry & enzymology
  - Cell & molecular biology
  - Immune cell and in vivo models
  - In vivo efficacy and PK
  - Translational research
  - Bioanalytical chemistry
  - Computational & medicinal chemistry
- Broad target and disease experience
- 42 scientists
  - 2:3 PhD:BS/MS ratio
  - 65% pharma experience



- State of the art laboratory facilities and vivarium
- Adjacent to Washington University Medical School and Barnes Jewish Hospital Complex
- Near St. Louis University School of Medicine

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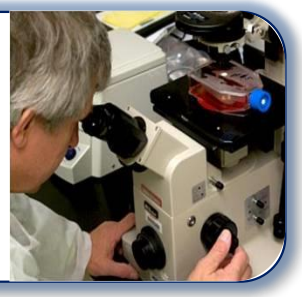
Platform - Research and Development Capabilities

BIOCHEMISTRY & ENZYMOLOGY

- Leaders in Mechanistic Enzymology
- Custom Assay Development
- Compound: Target Interaction
- Enzyme Inhibitor Mechanisms
- Direct Binding Kinetics
- High Throughput Screening

CELL & MOLECULAR BIOLOGY

- Target Clone/Express/Purification
- Translatable Cellular Assays
- Target Modulation/Disease Assays
- Cell Pathway Interrogation
- Custom Assay Development
- Multiple Assay Platforms



TRANSLATIONAL RESEARCH

- Biomarker Assay Development
- Clinical Biomarker Assessment
- *In vivo* Efficacy and PK Studies
- PK/PD Relationship
- Release Assay Validation

IMMUNOLOGY & IMMUNO-ONCOLOGY

- Cytokine Expression
- Th Cell Differentiation/Activation
- CTL Differentiation and Function
- B Cell and NK cell Function
- Ag Specific Cell and *In Vivo* Models
- HWB/PBMC/Monocyte Assays

BIOANALYTICAL CHEMISTRY

- Non-GLP Analytical
- Bioanalytical Method Development
- Bioanalytical Method Validation
- Pharmacokinetic/Toxicokinetic Analysis
- Ab Solubility and Aggregation

COMPUTATIONAL & MEDICINAL CHEMISTRY

- Schrödinger ™ Enabled Structure Based Drug Design
- Computational Chemistry
- Library Design
- Compound Synthesis

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Kinase Opportunity–Rational Targeted Drug Discovery

Creating New Medicines Targeting Previously Inaccessible Parts of the Kinome

KINect™ Technology Platform

Proprietary chemical library and integrated capabilities for interrogating the Kinome

- Solves challenges encountered in the class
  - Selectivity
  - Biochemical efficiency
- Validity of targeting kinases is commercially established
- Plethora of validated kinase targets are inadequately drugged
- Kinect™ platform allows rational targeting of validated kinase targets

Kinase Drugs Represented $240B in Aggregate Global Sales from 2011-2015

500 member class, representing 2% of the human genome

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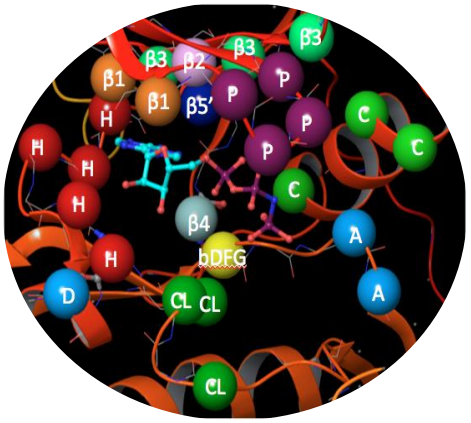
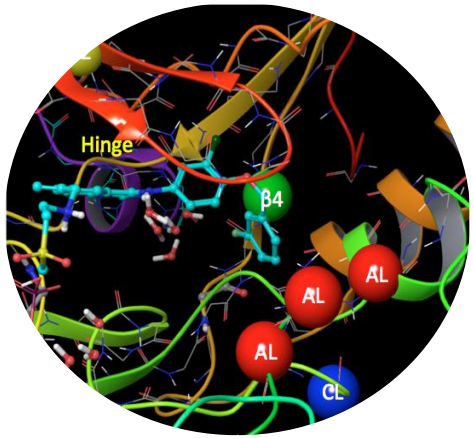
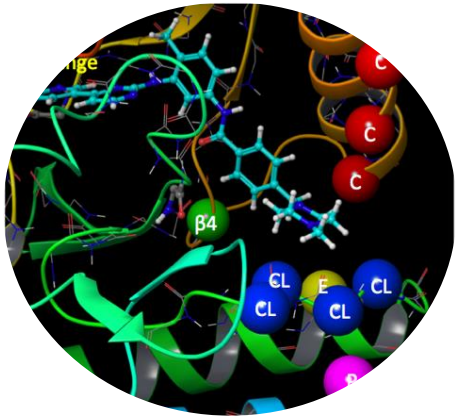
Platform - KINect™ Innovation Engine



Type 1 active conformation
215 cysteine kinases

Type 1.5 C-helix out conformation
68 cysteine kinases





Type 2 DFG out conformation
128 cysteine kinases

- Concentrated effort in immunology: autoimmune disease and chronic inflammation
- Cysteinome targeted chemical library (60% of the kinome)
- Focused on a number of important but hard-to-drug kinases
- Structural analysis, KINect™ chemical library, screening in validated bioassays, SBDD (Schrödinger enabled) and medicinal chemistry
- KINect™ library interrogates both Type 1 and Type 2 kinases vs competitors who focus only on a few subgroups of Type 1 kinases
- KINect™ addresses both reversible and irreversible inhibitors

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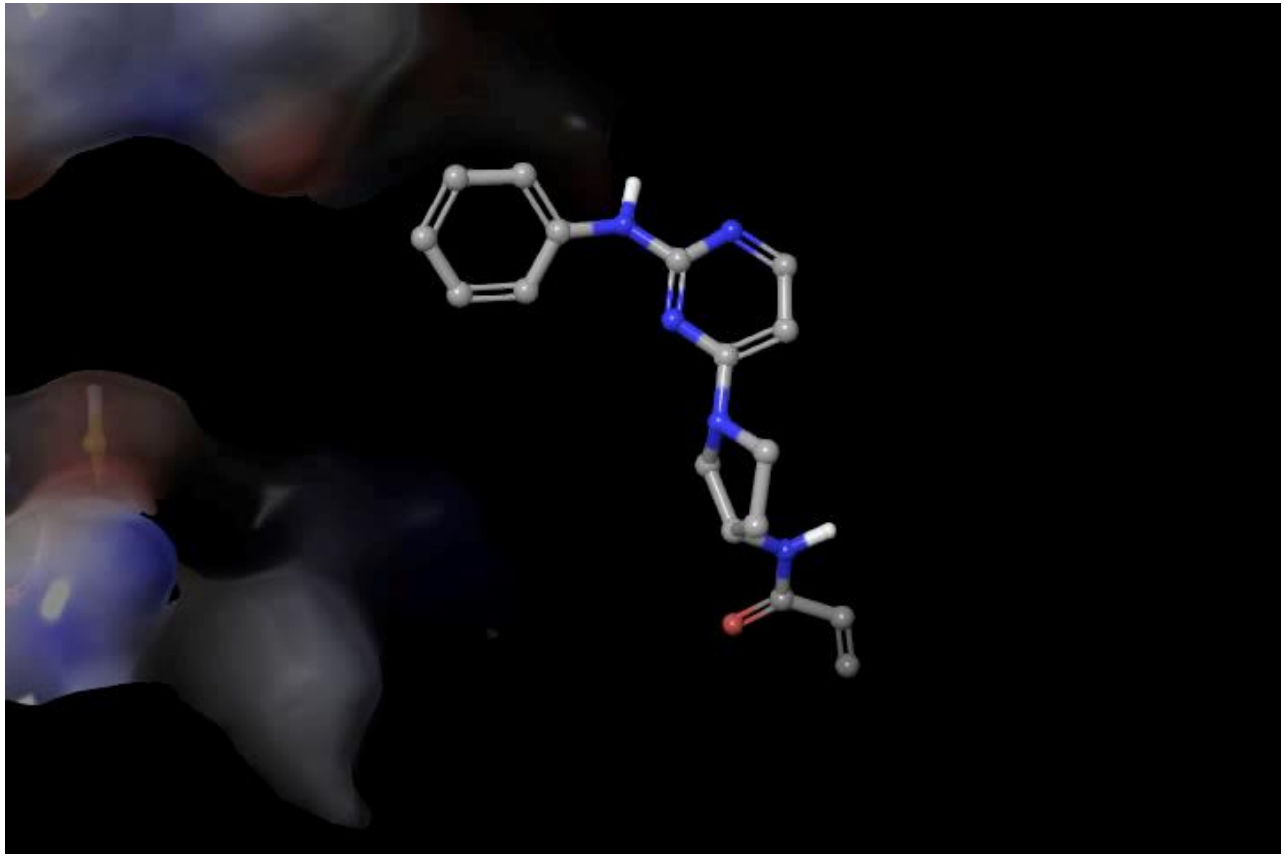
KINect™ Discovery of Covalent Kinase Inhibitors

- Leverage interaction with cysteine free -SH to address issues of potency, selectivity and biochemical efficiency
- Precise placement of reactive group provides enormous rate enhancement for covalent bond formation
- **Maximizing** reversible affinity and **Minimizing** reactivity to result in efficacious and safe drugs



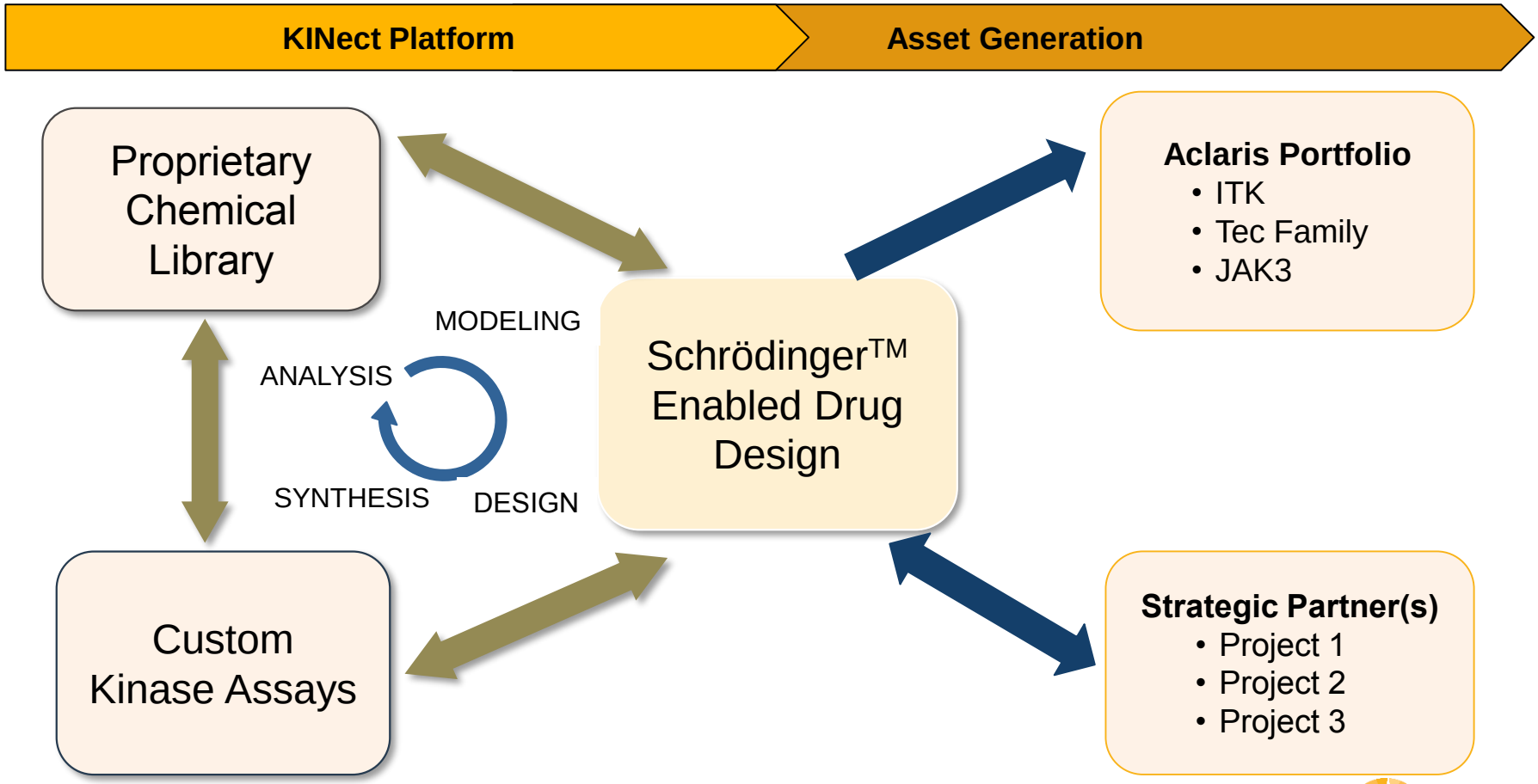
Kinase + KINect Library Compound

Reversible → ***Covalent***

Reactivity

KINect™ Technology Platform

Sustainable Asset Generation for Strategic Partnerships



Kinase Inhibitors for Dermatology

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CHARTING NEW TERRITORIES IN KINASE DRUG DISCOVERY

Quality Research Partners from IDEA to IND

Key Aclaris Kinase Targets

- Innate immune system
  - p38/MK2 pathway inhibitors (TNFα, IL1β)
    - Oral “anti-TNF & anti-IL1β”
- Adaptive immune system
  - Cytokine receptor kinases
    - JAK kinase inhibitors (IL4, IL15, IFNγ)
  - T-cell and B-cell receptor kinases
    - TEC kinase inhibitors (includes ITK, BTK)
      - ITK kinase inhibitors (T-cell receptors, Th17)
        - Oral/Topical “anti-IL17”

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Kinases are Validated Drug Targets

- Clinically validated cytokine receptor kinases - JAK kinase inhibitors
  - Tofacitinib/Xeljanz® (JAK1/3/2)
  - Ruxolitinib/Jakafi® (JAK1/2)
  - Multiple other JAK inhibitors in development
- T- and B-cell receptor kinases - ITK kinase inhibitors
  - Antigen receptor pathway inhibitors are clinically validated (ibrutinib/Imbruvica®; cyclosporin A /Neoral®, FK506/Prograf®, CTLA4Ig/Orencia®)
    - Ibrutinib (Imbruvica®) inhibits BTK
  - ITK kinase (interleukin-2-inducibleT-cell kinase)
    - Th17 and IL17 are clinically validated targets in psoriasis (Stelara®, Cosentyx®, Taltz®, Siliq®)
    - ITK is highly expressed in Th17 cells
    - ITK inhibitors block Th17 cell differentiation and expression of IL17

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Aclaris Tool Kit of Kinase Inhibitors

- Non-covalent (reversible) inhibitors which target any of the four JAK kinases associated with cytokine receptors (JAK1, JAK2, JAK3, TYK2)
- Covalent (irreversible) inhibitors of JAK3
- Covalent (irreversible) inhibitors of ITK
- Covalent (irreversible) inhibitors that simultaneously target JAK3 and ITK

Creating potent molecules with the optimal physicochemical properties for:

- *oral delivery* enables Aclaris to target multiple moderate-to-severe dermatologic diseases
- *topical delivery* (coupled with Aclaris' formulation expertise) enables us to target any inflammatory dermatologic disease

JAK Kinases as Drug Targets - History

- David Vetter (9-21-71 to 2-22-84)
- The original ”bubble boy”
- 1993: Leonard & O’Shea labs define genetic basis for severe combined immunodeficiency disease (XSCID and SCID)
- Mutations of JAK3 kinase or γc receptor lead to defective signaling by 6 cytokines
- If goal is maximal immune suppression, could this be a new drug for renal transplant? (YES!)
- If goal is moderate suppression of immune response, could this be used for chronic autoimmune disease?

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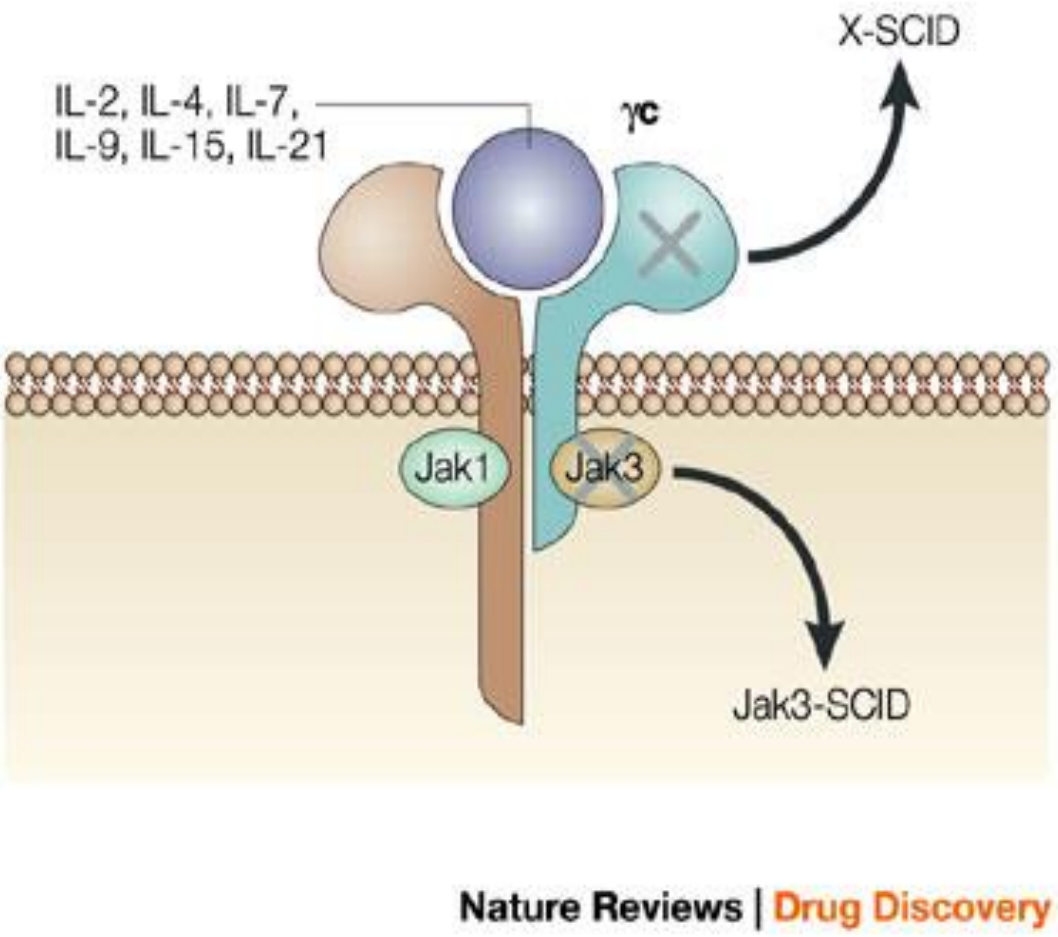
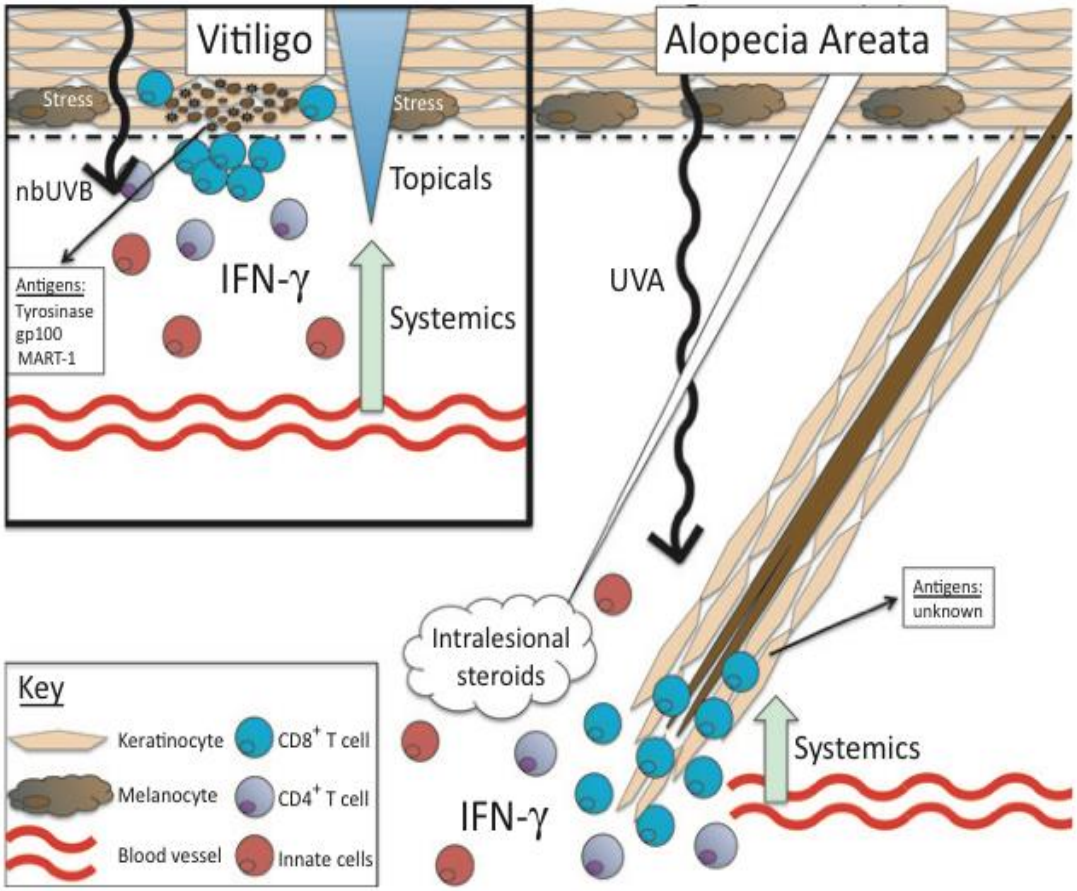
SCID Biology Teaches Role of JAK3 and JAK1

- SCID patients lack JAK3 congenitally – but JAK3 receptors **require** JAK1
- Family of 6 cytokines controlled by these two kinases involved in normal and inflammatory immune response
- Autoimmune diseases in general, but dermatological diseases in particular, strongly influenced by **IL-4 and IL-15**
- Systemic therapy effective, however – topical drug delivery offers skin-targeted site of action

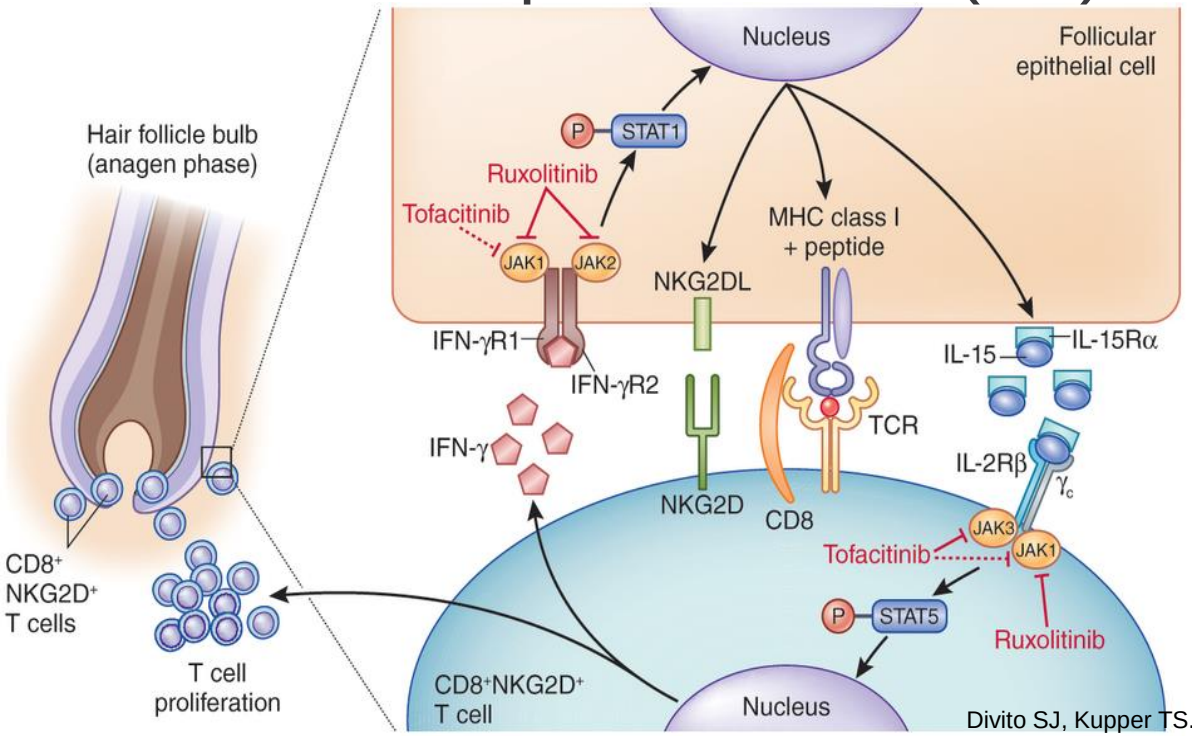


Treating Systemic Skin Diseases Topically

- Autoimmune skin diseases are known to be systemic in nature, however…
- Systemic immunosuppressants often indicated for severe disease
- “Soft approach” – drugs designed for rapid metabolism after passage through skin
- Topical drugs have potentially broader use among mild to moderate disease
- Potency and selectivity enhanced with kinase crystal structure availability
- Differential formulations allow penetration to relevant skin layers



JAKs and STATs of Alopecia Areata (AA)



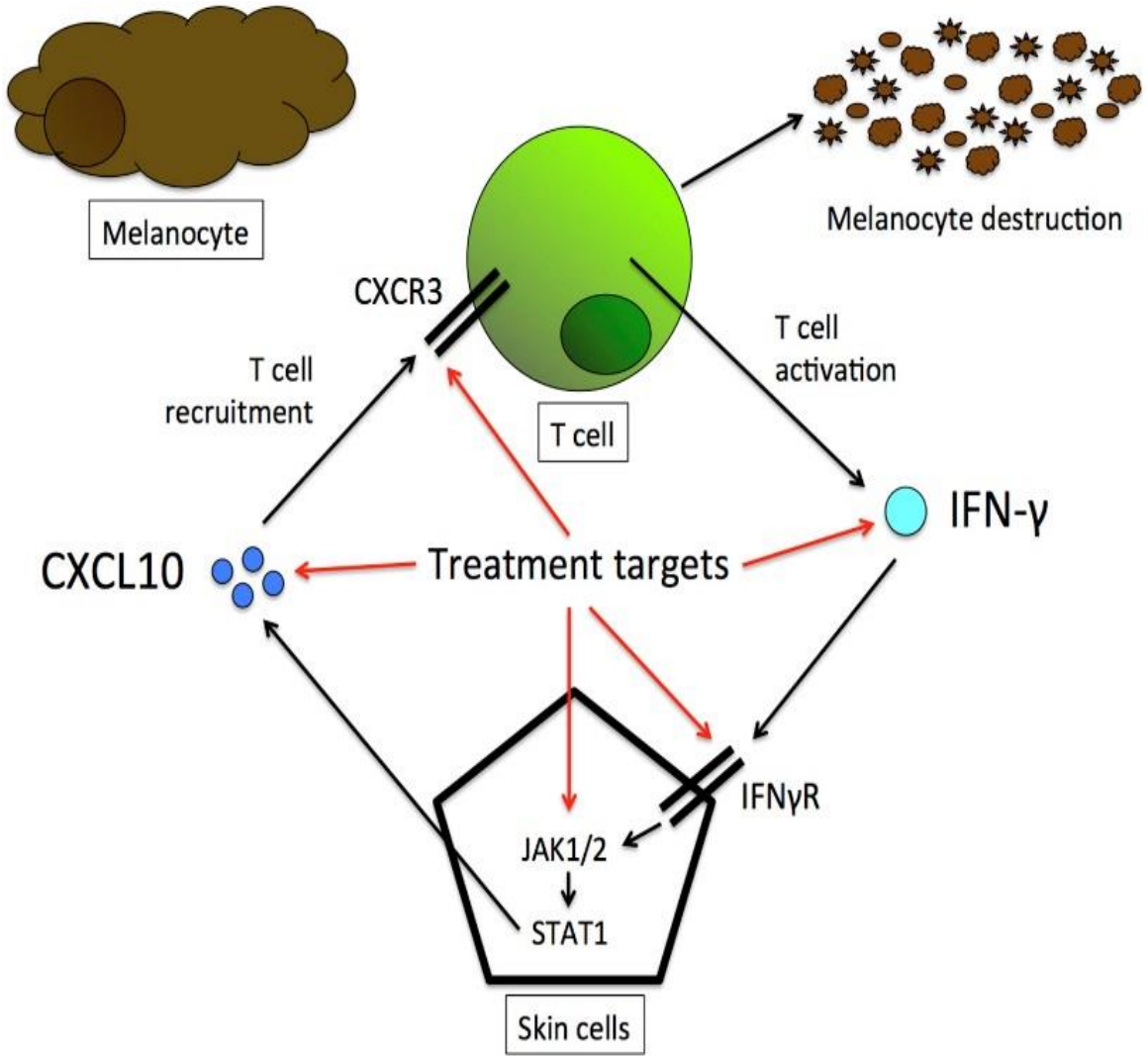
Divito SJ, Kupper TS. Nat Med. 2014 Sep;20(9):989-90

- Alopecia Areata: Patchy hair loss, primarily of the scalp
- A positive feedback loop between activated CD8+ lymphocytes producing IFNγ and follicular epithelial cells producing IL-15 is found in the skin of AA patients.
- The end result of this amplification is activated CD8+ CTL cells which attack the hair follicle bulb – leading to the hair loss seen in patients.
- Clinical validation of this approach has been achieved with systemic use of marketed JAK inhibitors (tofacitinib and ruxolitinib)

Xing/Christiano/Clynes) Nat Med. 2014 Sep;20(9):1043-9

JAKs and STATs of Vitiligo Pathogenesis

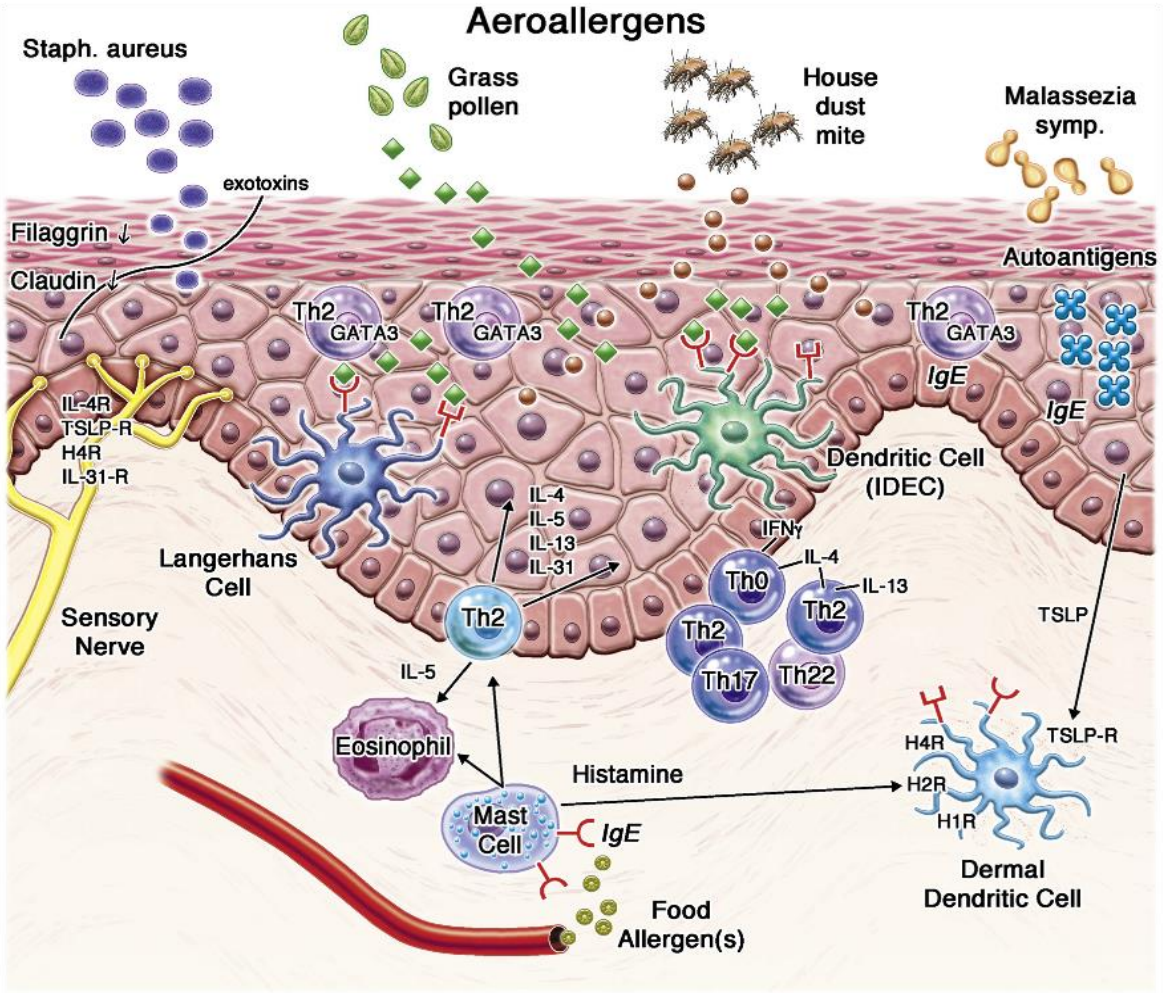
- Vitiligo: autoimmune attack on epidermal melanocytes leading to loss of skin pigmentation
- Melanocyte cellular stress activates innate immunity, resulting in recruitment of T cells
- T cells specific for melanocyte auto-antigens are found in the skin and blood of patients
- CD8+ T cells producing IFNγ are necessary and sufficient for disease
- Clinical validation of this approach has been achieved with systemic use of marketed JAK inhibitors (tofacitinib and ruxolitinib)



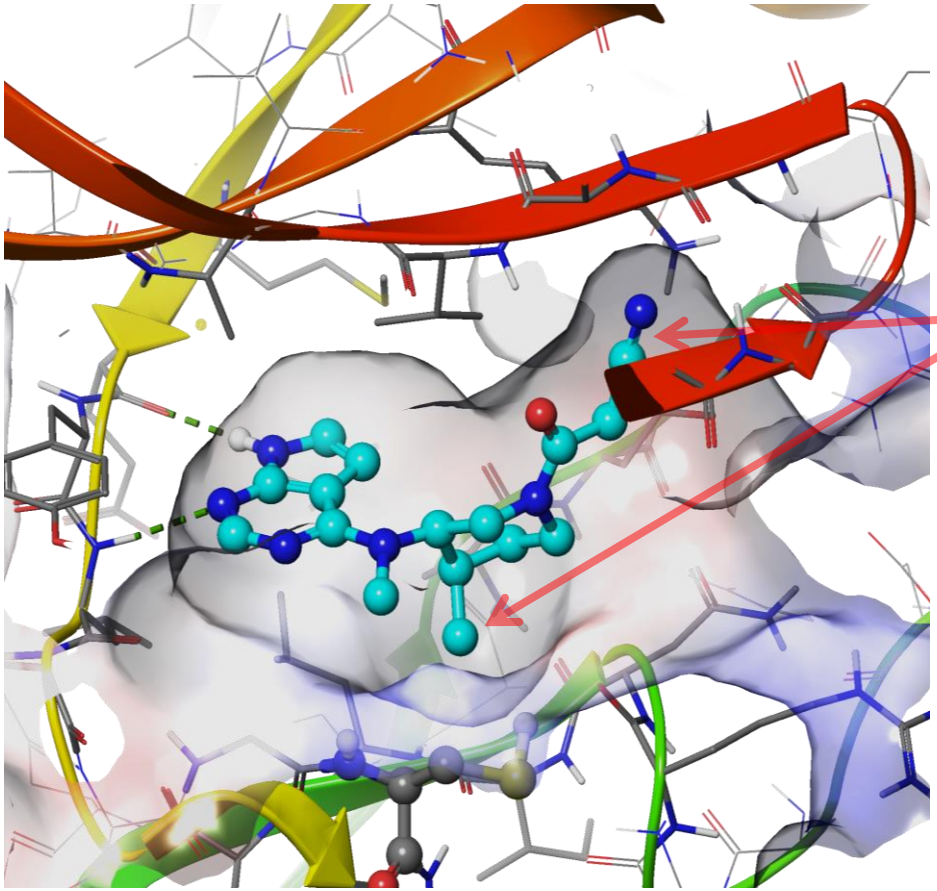
Harris et al, J Am Acad Dermatol 2017;77:1-13.

JAKs and STATs of Atopic Dermatitis (AD)

- AD is strongly driven by Th2 cells → IL-4/13
- IL-4R uses JAK1/3 and IL-13R uses JAK1/2
- Baricitinib (JAK1/JAK2) and upadacitinib (JAK1) have shown efficacy in Phase II AD trials
- Dupixent® (dupilumab, Sanofi-Regeneron) antibody blocks both IL-4/13
- AD also has Th17 signature – IL-17A and IL-22 – targetable with ITK inhibitors



JAK3-Tofacitinib Structural Lessons



JAK3-tofacitinib structure 3LXK, 2.0 Å

- Tofacitinib crystal structures in other JAK family members are similar
- Chiral linker provides significant 3D shape
- Ceiling and floor interaction motif provides unusual kinase specificity for the JAK family
  - Methyl group induces JAK-family specificity pocket
- Numerous published crystal structures of JAK inhibitors also inform design efforts
- Using structure-based drug design to prepare JAK-selective inhibitors
- Leads for topical application are metabolically labile, resulting in limited systemic exposure

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Optimal JAK Profile and Drug Properties

- Broad JAK inhibitor acceptable – selectivity over JAK2 desired
- Potency not critical but need to be able to formulate appropriately – adjust as structure-activity relationship (SAR) evolves (Enzyme < 20nM; Cell < 300nM)
- Good kinome selectivity
- Acceptable duration of action
- For topical JAK inhibitors
  - Acceptable skin permeability (measure Jmax on standards and advanced compounds)
  - Acceptable duration of action in skin
  - Rapid cleavage by enzymes in plasma/liver

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Optimal Topical JAK Profile and Drug Properties

Criteria	Target Value	Status
JAK1 or JAK3 enzyme assays	<20 nM	Achieved
JAK cell assays (IL2-STAT5)	<300 nM	Achieved
Predicted skin permeability	Log Kp < -4	Achieved
Metabolically labile	$T_{1/2}$ <30 min	Achieved
High aqueous solubility	>100 uM	Achieved
Permeability (PAMPA)	Pe > 5 nM/s	Achieved
Kinome selectivity	SI < 0.1	Achieved

- Potent and selective inhibitors in enzyme and cell have been identified
- Metabolically labile once in circulation - incorporating a metabolic handle into a topical drug such that it is rapidly metabolized once it hits the bloodstream
- Excellent solubility
- Key compounds being scaled for efficacy studies

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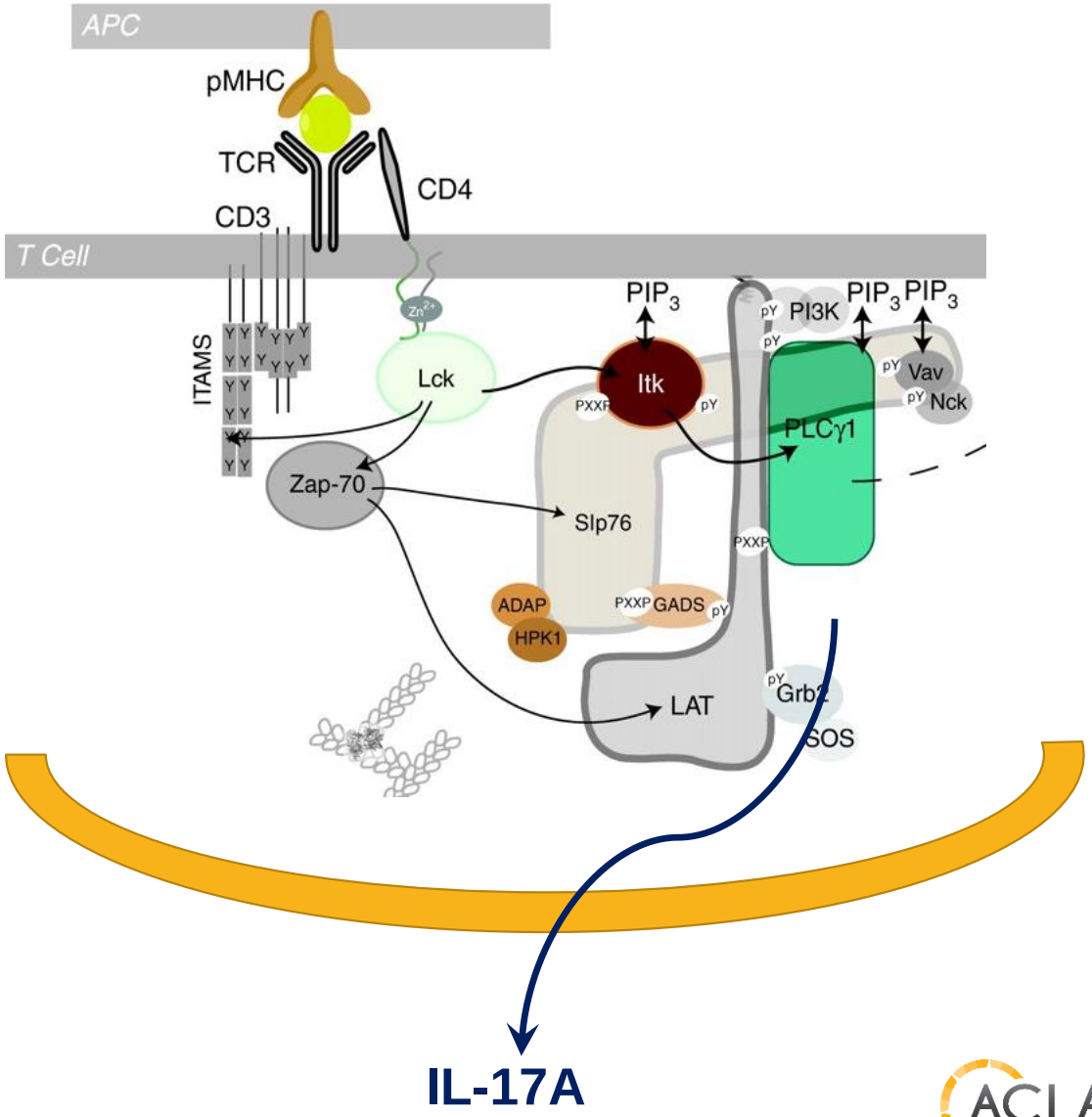
TEC Kinases as Drug Targets

- “Druggable” class of kinases activated by both T cell and B cell receptors
- Inhibitors of ITK act as small molecule inhibitors of Th17 and Th1 cells, primary drivers of autoimmune disease
- Evaluation of both topical and oral approaches



Key Role of Th17/Th1 Axis in Psoriasis

Psoriasis Biology/Current Rx

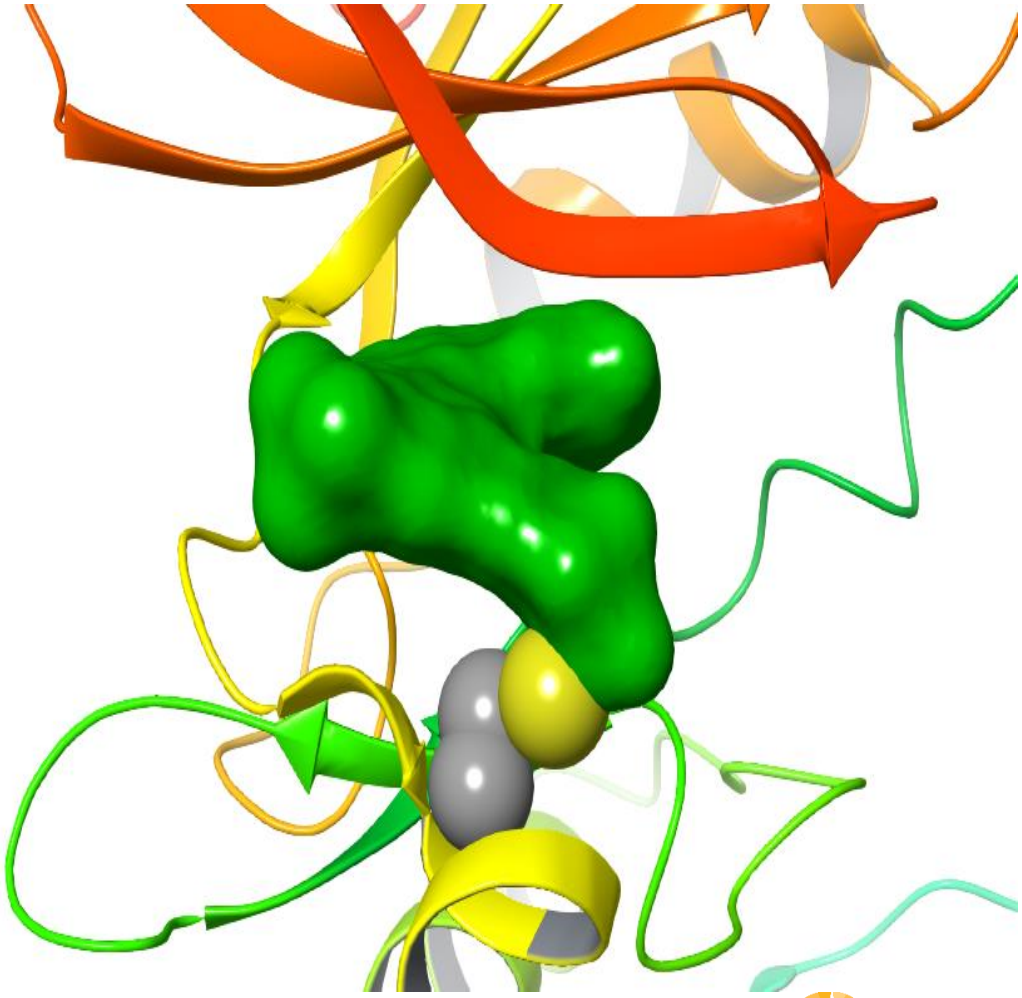
- Increased numbers of T cells and levels of IL-17 and IFNγ in psoriatic lesions
- IL-12/23 blockade (Stelara®, ustekinumab, Janssen) limits differentiation into Th17 and Th1 – the cells making IL-17A and IFNγ
- Anti-IL-17A (Cosentyx®, secukinumab, Novartis) blocks IL-17A action

Aclaris Psoriasis Strategy

- Confluence ITK inhibitors will be designed to do BOTH:
  - Decrease differentiation into Th17 and Th1 cells
  - Limit production of IL-17A and IFNγ
- Net result: Reduced keratinocyte activation and lymphoid inflammation

Aclaris ITK Program

- X-ray data has been critical to structure-based drug design efforts
- High resolution ITK structure 1.25Å (unpublished)
- Covalent attachment of ligand confirmed



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Optimal Topical ITK Profile and Drug Properties

Criteria	Target Value	Status
ITK enzyme assay	<10 nM	Achieved
ITK cell assay (Jurkat PLCg1)	<500 nM	Achieved
ITK/BTK selectivity in cell	>10x	Achieved
Predicted skin permeability	Log Kp < -4	Achieved
Metabolic instability – liver microsomes or hepatocytes	$T_{1/2}$ <30 min	Achieved
High solubility	>100 uM	In Process
Permeability (PAMPA)	Pe > 5	In Process

- Potent inhibitors in enzyme and cell have been identified
- Selective over BTK in cell
- Metabolically labile once in circulation
- Key compounds being scaled for efficacy studies

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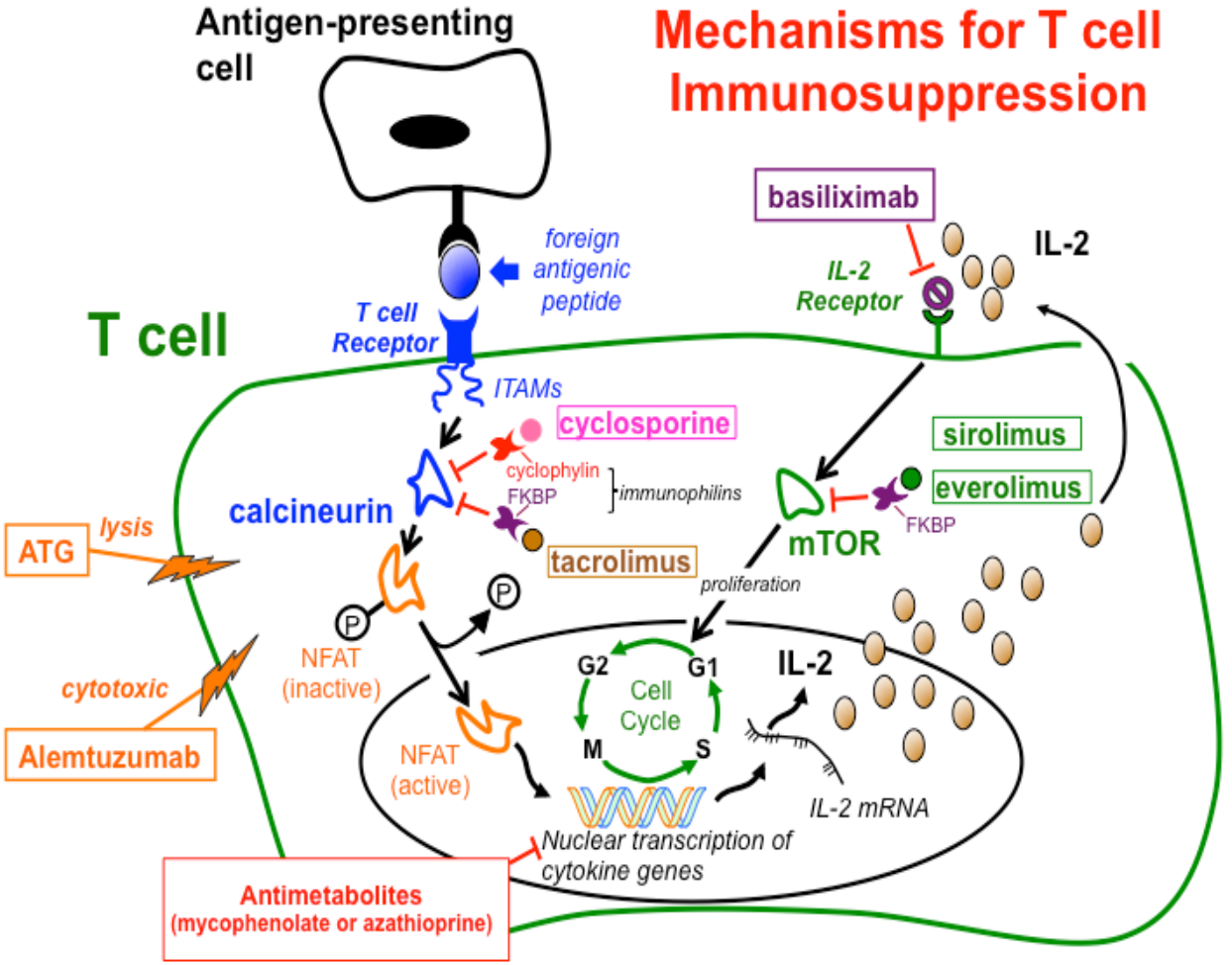
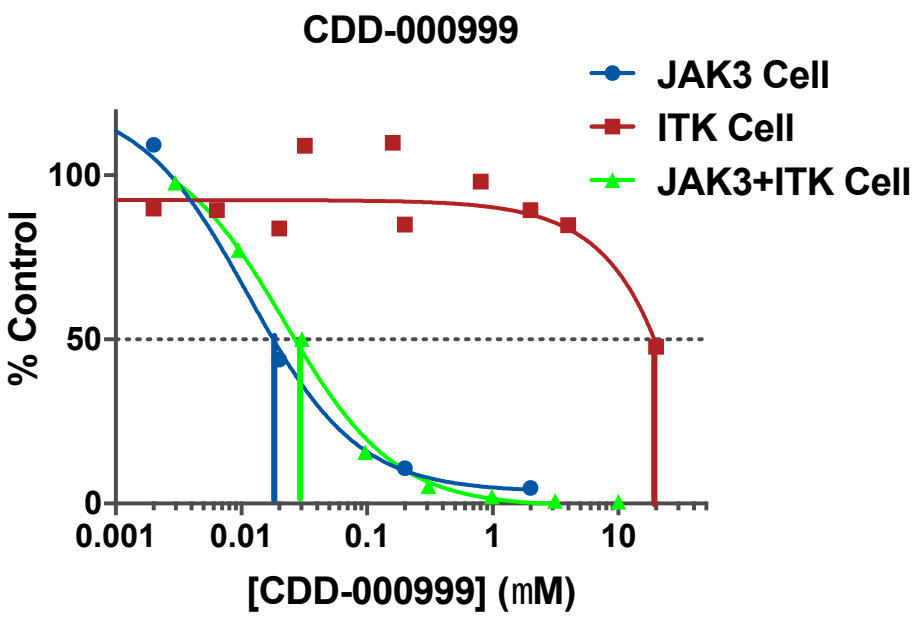
Synergistic Block of T Cell/Cytokine Receptors (ITK & JAK3)

- Organ transplant field shows that blockade of multiple nodes of T cell activation provides synergy
- Like transplant, autoimmune diseases driven by **both** T cell and cytokine receptors
- Single molecules have capacity to inhibit both the TCR receptor (ITK) and the IL-2 receptor (JAK3)

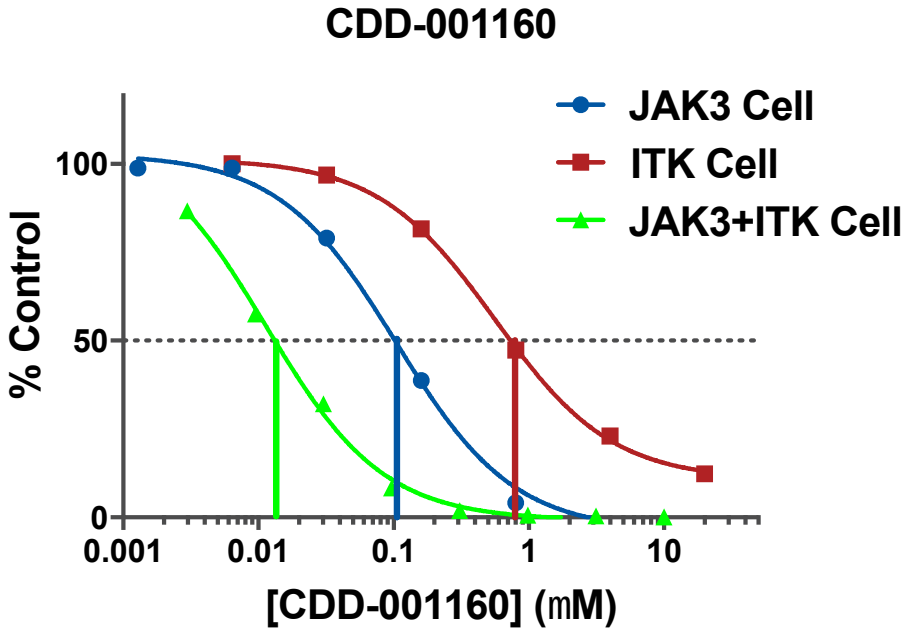


Synergy of Dual Inhibitors of JAK3 and ITK

Non-Covalent JAK3 Inhibitor



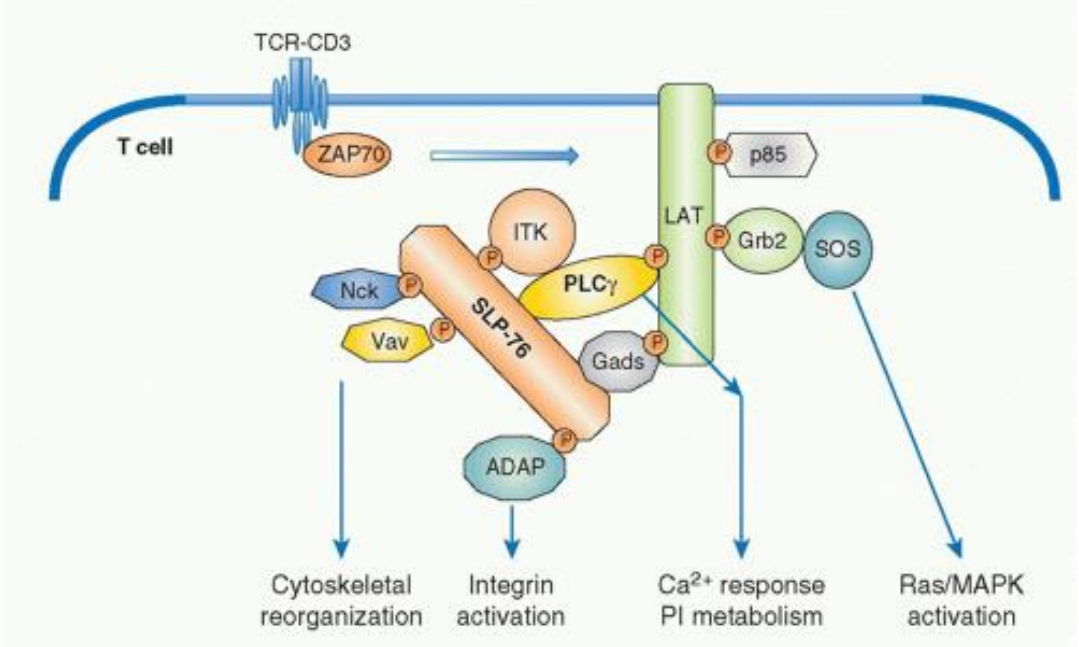
Covalent JAK3/ITK Inhibitor

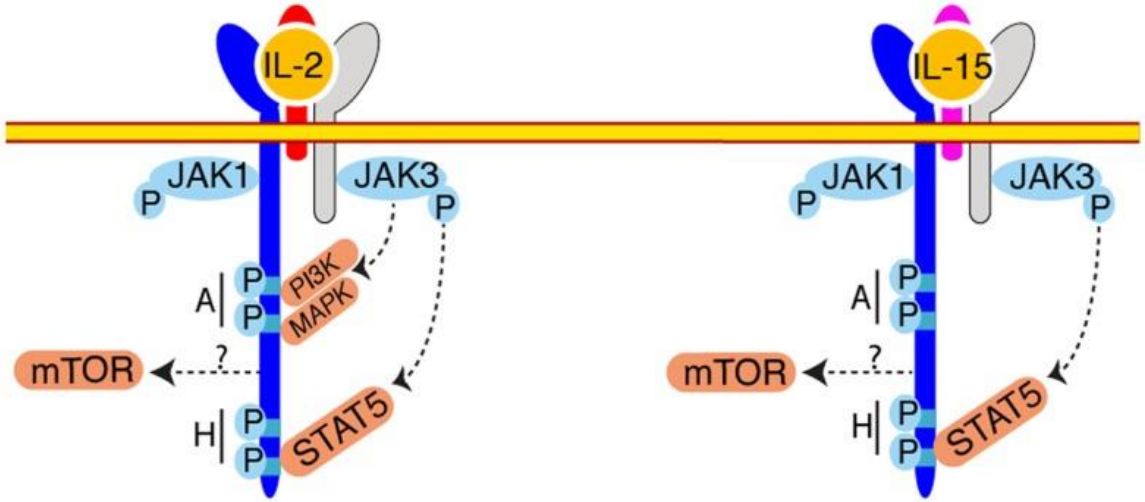


- Red and Blue lines depict cellular assays dependent on T cell (ITK) and cytokine (JAK3) receptors, individually.
- Green line shows potency of compounds in cells driven by simultaneous activation of both T cell and cytokine receptors.
- Only dual JAK3/ITK covalent inhibitor demonstrates increased potency - relative to individual assays - in cells driven by both T cell and cytokine receptors.

Rationale for JAK/ITK Inhibitors in Dermatology

- Autoimmune disease dependent on CD4 and CD8 cells
- Autoantigens in dermatologic diseases found to activate T cell receptors
- **ITK** is tyrosine kinase downstream of TCR with restricted expression
- Activated T cells produce numerous cytokines, including IL-15 found in skin
- **JAK3** is required for signaling by the IL-15 receptor
- Aclaris has found covalent inhibitors that simultaneously target ITK and JAK3





Summary – JAK & ITK programs

- The discovery of tofacitinib (Xeljanz®) for autoimmune disease was the result of almost two decades of hard work – and a fair bit of serendipity
- At Aclaris, structure-based drug design is used to drive chemistry in both JAK and ITK programs
- *In vivo* evaluation of leads is in progress
- Aclaris has an inventory of reversible & irreversible (covalently binding) JAK & ITK inhibitor leads that have been specifically designed for either oral delivery or as “soft” topical drugs

ACLARIS THERAPEUTICS

ATI-450 A Small Molecule Inhibitor of TNFα and IL-1 BioSynthesis

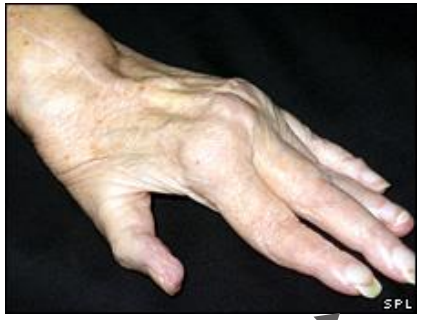
Confluence
DISCOVERY TECHNOLOGIES
A Wholly Owned Subsidiary of Aclaris Therapeutics, Inc.

CHARTING NEW TERRITORIES IN KINASE DRUG DISCOVERY

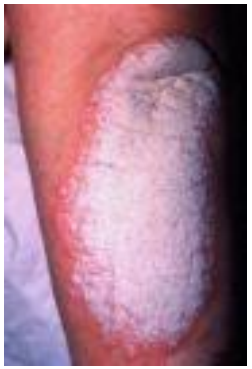
Quality Research Partners from IDEA to IND

Inflammatory Cytokines Drive Disease Pathophysiology

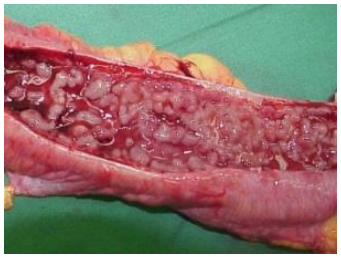
Rheumatoid Arthritis
Juvenile Idiopathic Arthritis



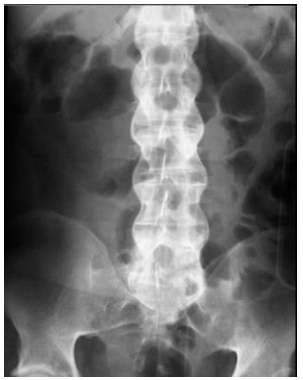
Psoriasis
Psoriatic Arthritis



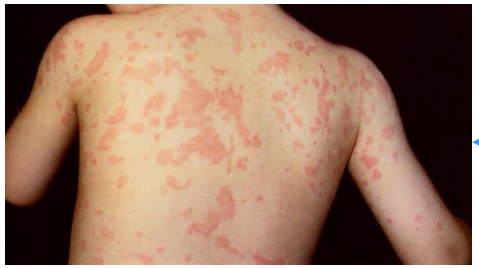
Inflammatory Bowel Disease



Ankylosing Spondylitis



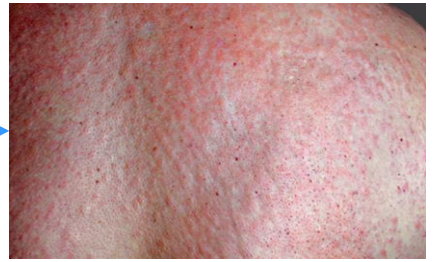
CAPS / Autoinflammatory Disease



TNFα

IL-1

Still's Disease



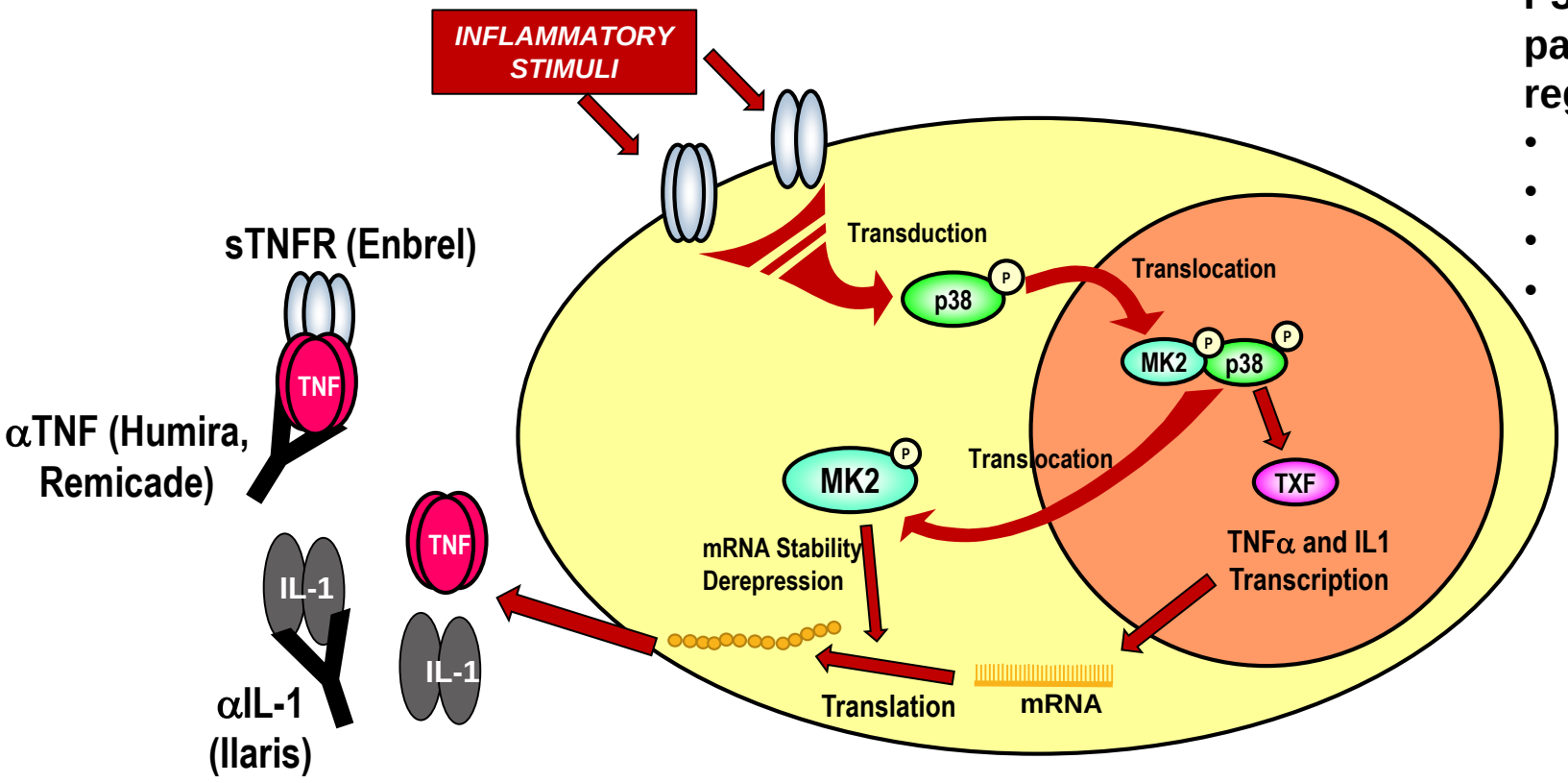
Anti-TNF Biologic Drugs: Humira®, Enbrel®, Remicade® (>$30B sales)
Anti IL-1 Biologic Drugs: Kineret®, Ilaris®, Arcalyst® (~$1B Sales)

Opportunity: an oral drug with efficacy paralleling anti-TNF and anti-IL1 biologics

ACLARIS THERAPEUTICS

Intracellular Pathways Regulate Cytokine Production

p38/MK2 pathway required for IL-1 and TNFα biosynthesis

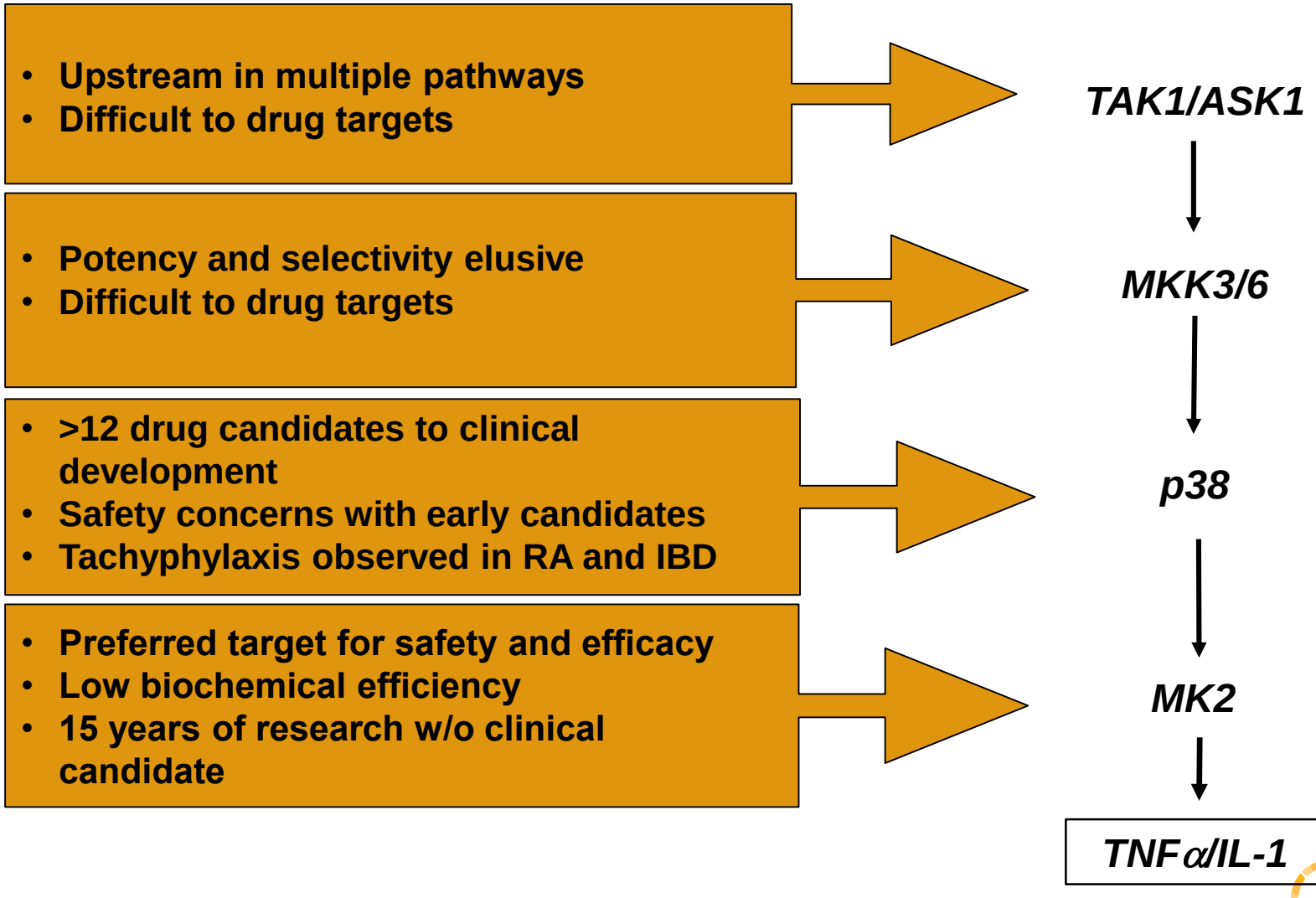


P38/MK2 pathway also regulates

- **IL-6**
- **IL-8**
- **COX-2**
- **iNOS**

Pharma Experience with the p38 Pathway

A novel approach to target the p38/MK2 pathway is needed

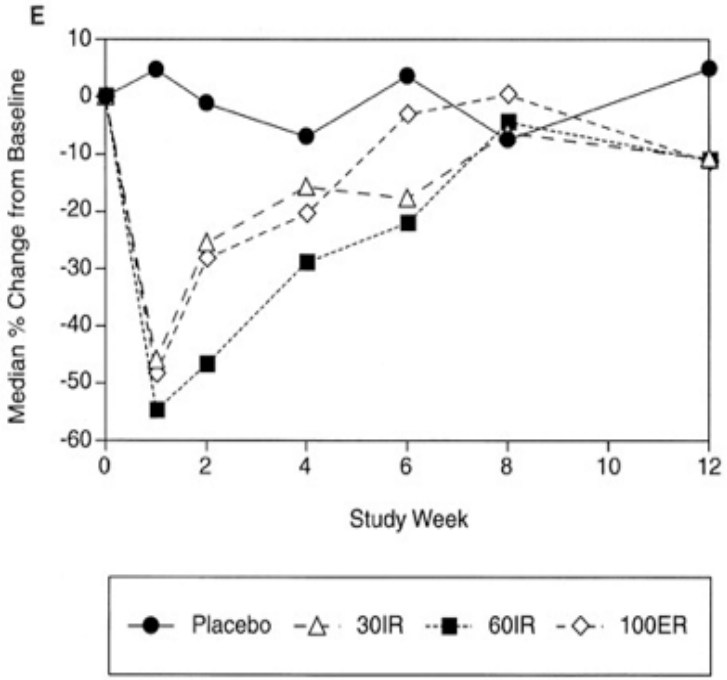


Challenge of Traditional p38 Inhibitors

Transient Efficacy or Tachyphylaxis

Tachyphylaxis: Rheumatoid Arthritis Study

JNJ/SCIO-469 CRP Levels

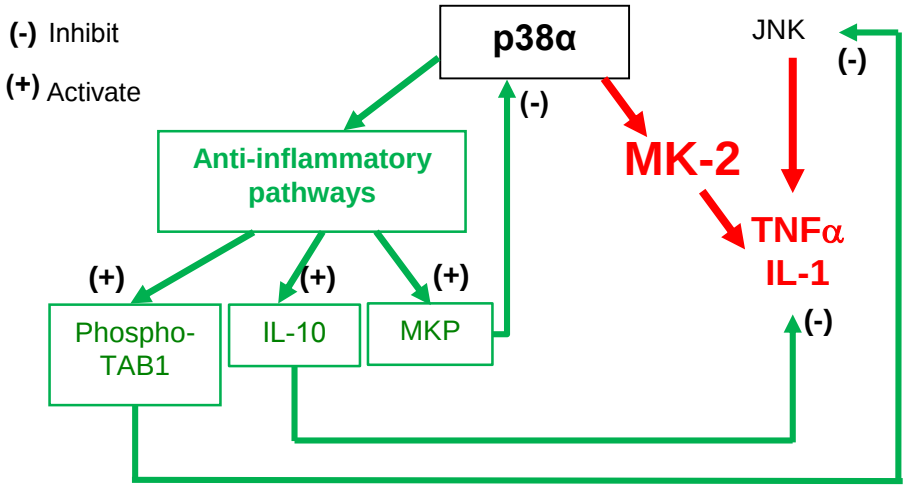


Genovese, et al., J Rheumatology (2011)

- Safety - Transient ⇑ LFT, Rash
- Transient Efficacy - No Go for RA
- Also seen in IBD, ACS

Hypothesis:

- Global p38 inhibition blocks inflammatory **and** anti-inflammatory pathways
- MK2 pathway inhibitor will maintain efficacy through selective inhibition of the inflammatory pathways

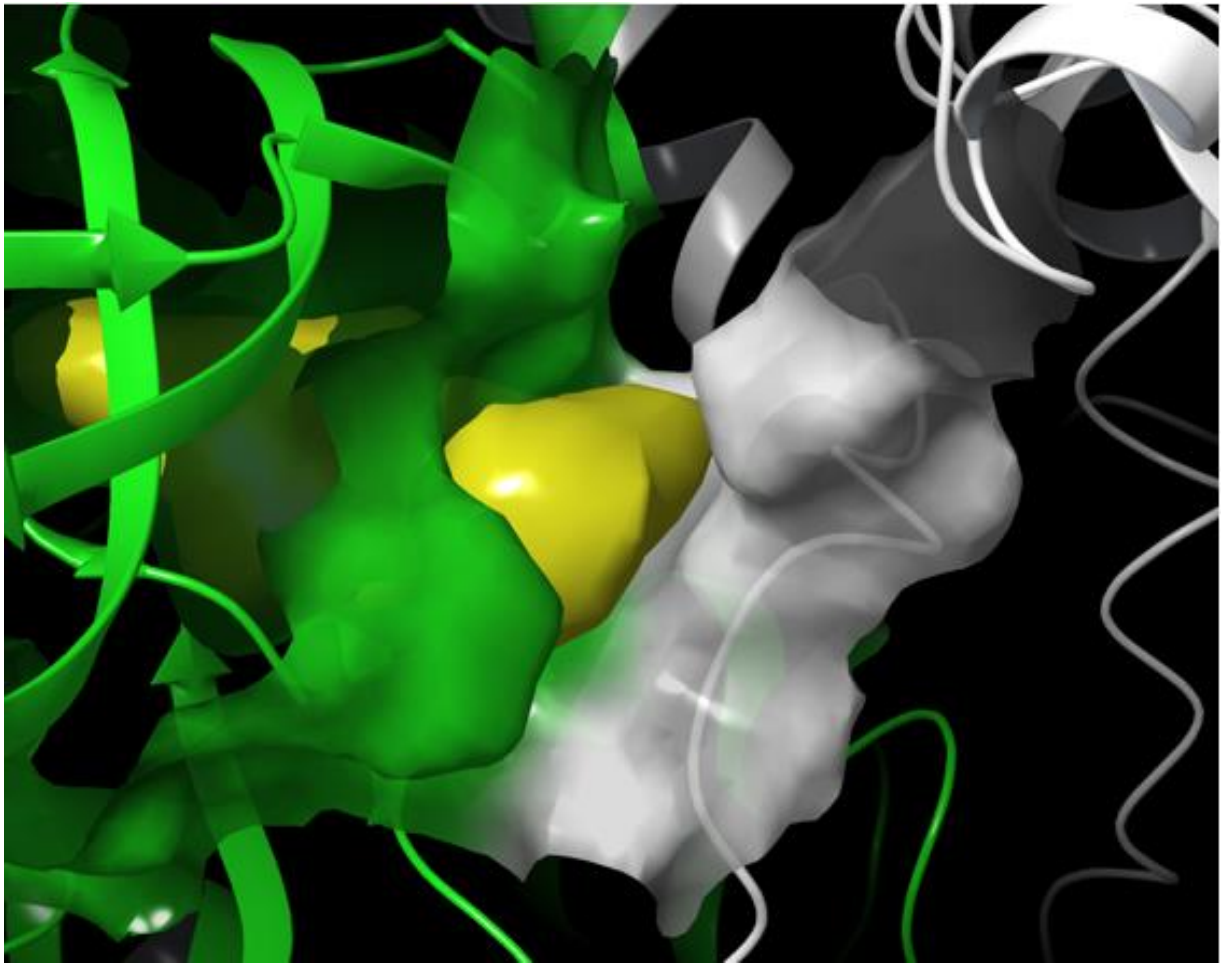


Schematic of MK2 dependent inflammatory pathway and other anti-inflammatory pathways downstream of p38MAPK

ACLARIS THERAPEUTICS

ATI-450 Selectively Inhibits the p38: MK2 Complex

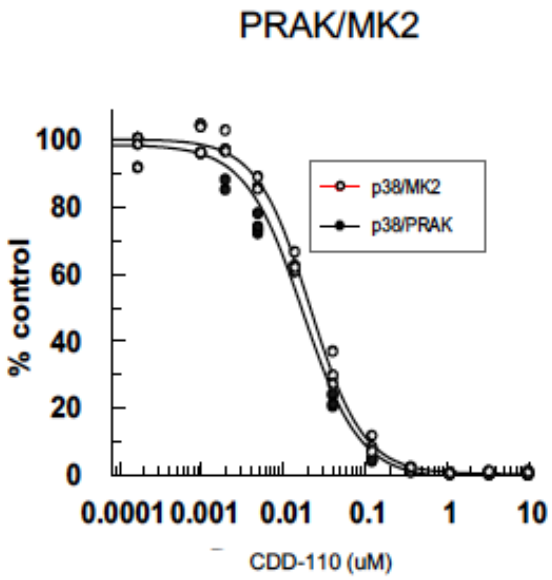
- Crystal structure of Interface between p38α/MK2 complex
- P38α: green MK2: white with docked model of ATI-450 (gold)
- ATI-450 binds to both the p38 and MK2 surfaces generating much higher affinity than to p38 alone
- Other p38 substrates have a distinct binding surface not recognized by ATI-450



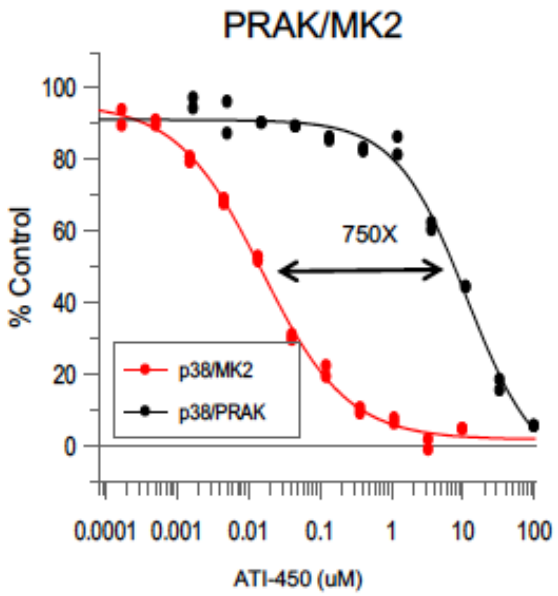
ACLARIS THERAPEUTICS

MK2 Pathway Inhibitor: ATI-450

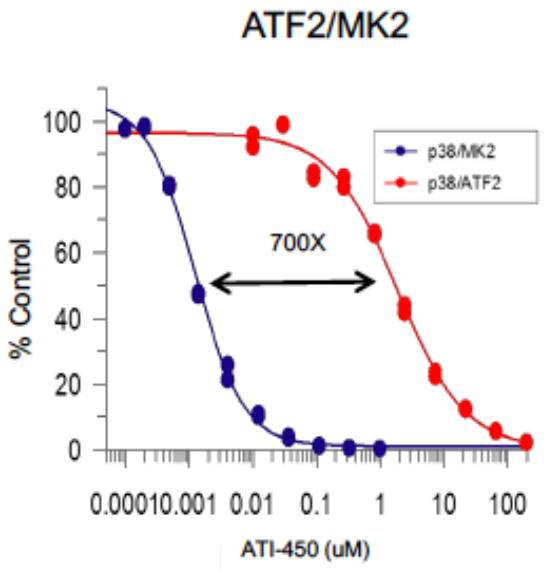
Demonstration of MK2 selectivity vs. other substrates



Global p38 Inhibitor



ATI-450

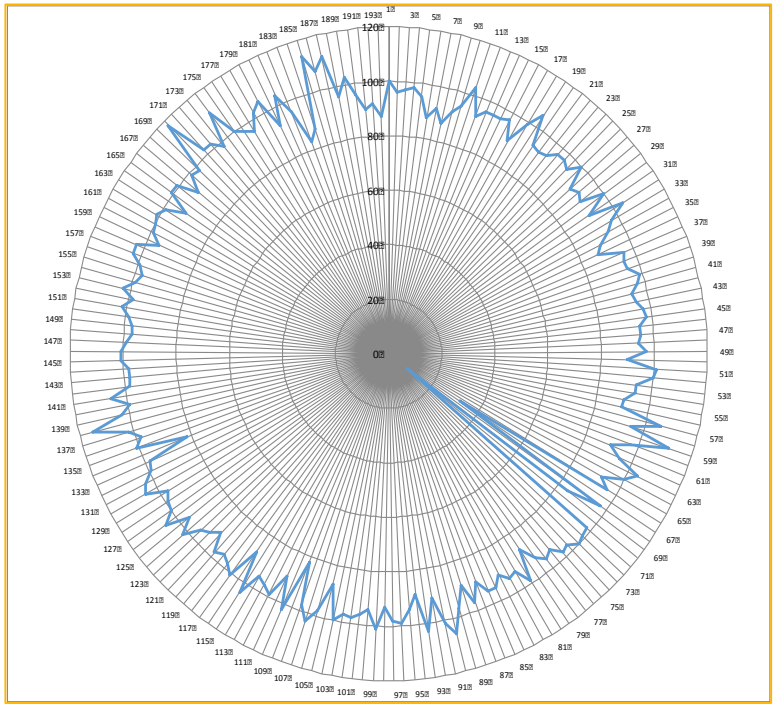


ATI-450

ATI-450 blocks p38-induced phosphorylation of MK2 ~700X more potently than representative downstream kinase (PRAK) or transcription factor (ATF2)

ATI-450 Selectivity - *Broad kinome and substrate selectivity*

KINOME SELECTIVITY



- ATI-450 tested vs 194 kinases at 5 μM
- >350-fold binding selectivity on all kinases except p38α and p38β

SUBSTRATE SELECTIVITY

Assay	IC_{50} nM	Fold Selective
p38/MK2	17	
p38/p38tide	855	51
MK2/HSP27	>10000	>550
Cellular Selectivity pHSP27 vs. pJNK		146
Cellular Selectivity pHSP27 vs. pCREB		12

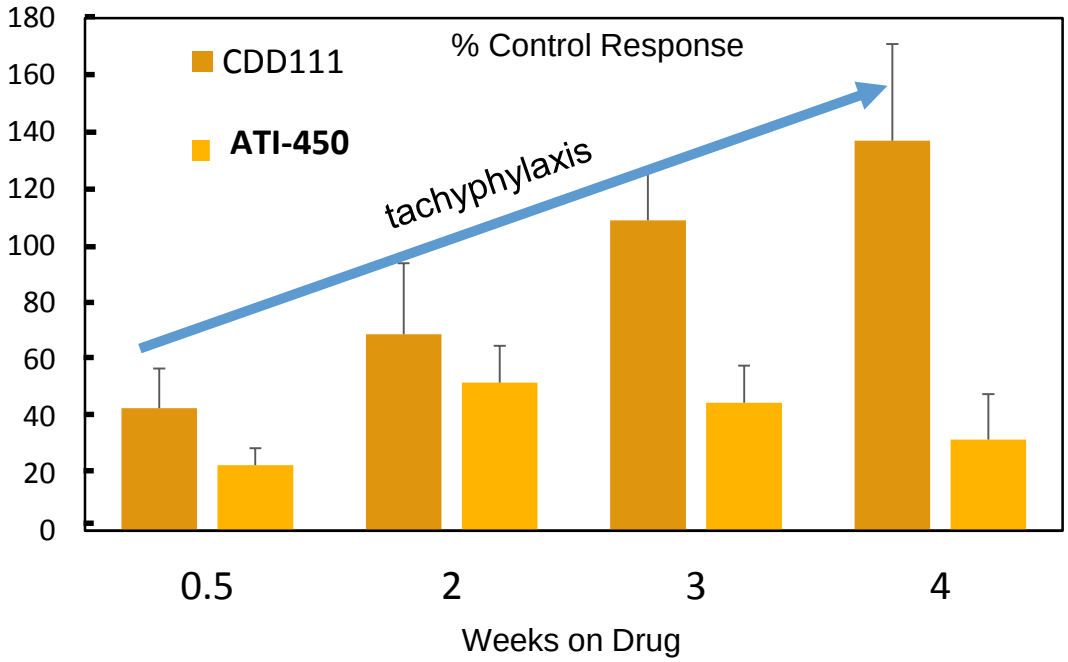
- ATI-450 is highly selective for the p38/MK2 complex vs. other p38 substrates, p38 alone or MK2 alone
- Significant shift in blocking pCREB or stimulating pJNK vs global p38 inhibitors

ACLARIS THERAPEUTICS

Mouse LPS-Induced TNFα Production

ATI-450 demonstrates durable response (no tachyphylaxis)

- Global p38 inhibitor CDD-111 lost efficacy as a function of dosing duration over 4 weeks
- This lack of durable efficacy is similar to that observed in IBD and RA clinical studies with global p38 inhibitors
- **The MK2 pathway inhibitor ATI-450 demonstrates durable efficacy in this model (no tachyphylaxis)**



- Conventional p38 (CDD-111) and MK2PI (ATI-450) administered to mice in feed starting day 1 and continuing through day 28
- At the day indicated mice were LPS challenged and blood TNFα levels determined

Animal Models Supporting ATI-450 Indications

- Rheumatoid Arthritis
  - Rat streptococcal cell wall arthritis model
- Cryopyrin Associated Periodic Syndromes (CAPS)
  - Murine NOMID (severe form of CAPS) transgenic model
  - Human CAPS patient IL-1β modulation
- IBD/Crohn's Disease
  - Murine colitis model

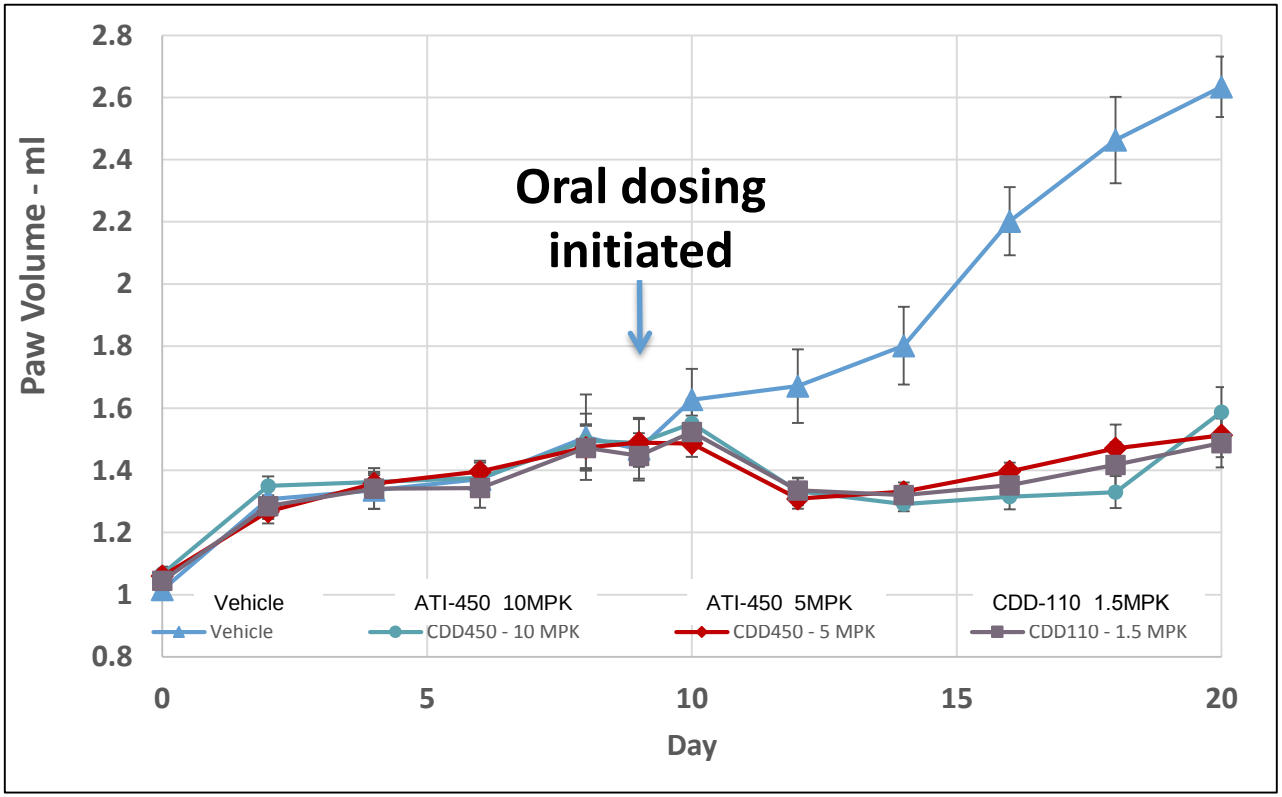
ATI-450 Efficacy in Rat SCW Arthritis Model

Therapeutic oral disease modifying efficacy

Anti-inflammatory Efficacy in Streptococcal Cell Wall Arthritis Model: Therapeutic Dosing

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.

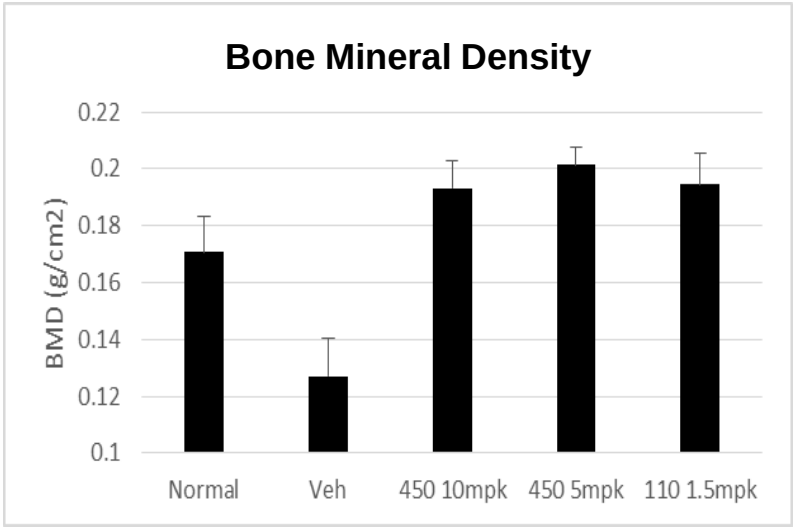


Efficacy comparable to global p38 inhibitor (CDD-110) and rat-enbrel (historical data)

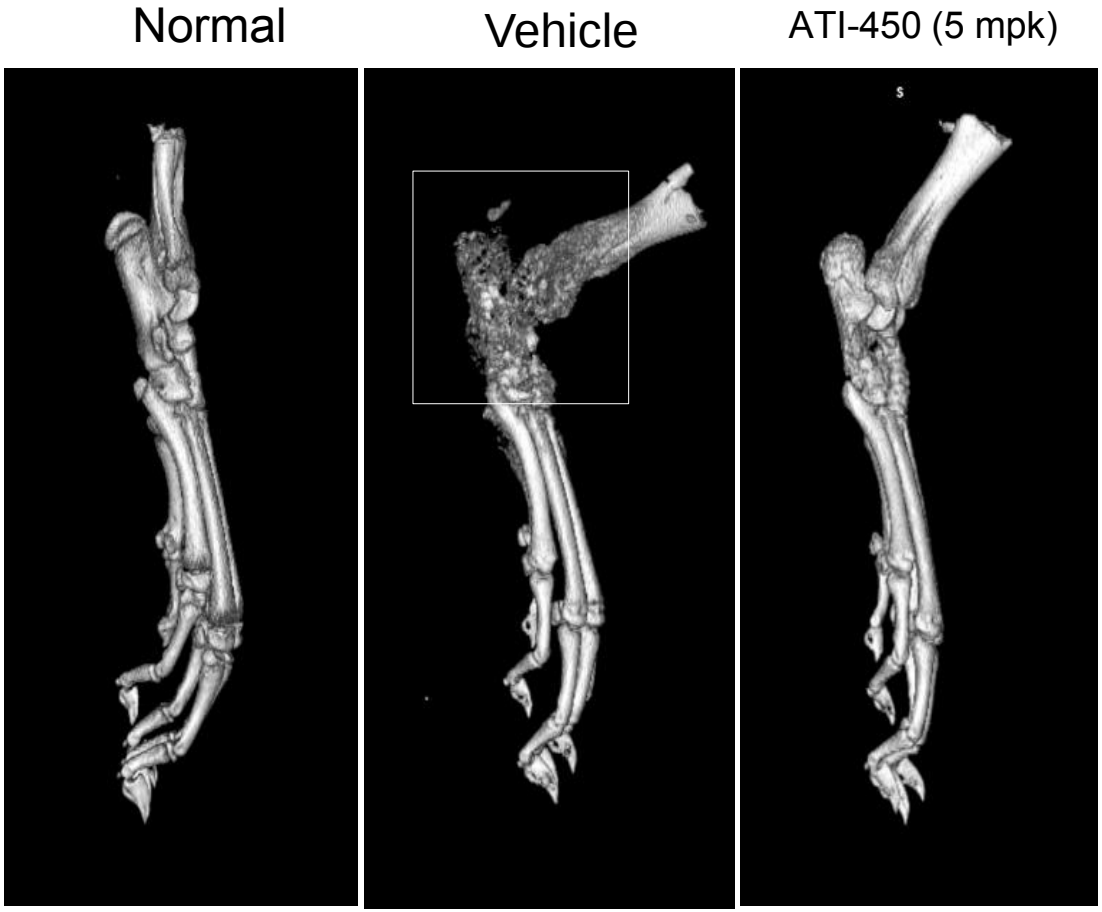
ATI-450 Efficacy in Rat SCW Arthritis Model

Disease modifying efficacy – Joint preservation

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



ATI-450 PROTECTS THE RAT ANKLE JOINT

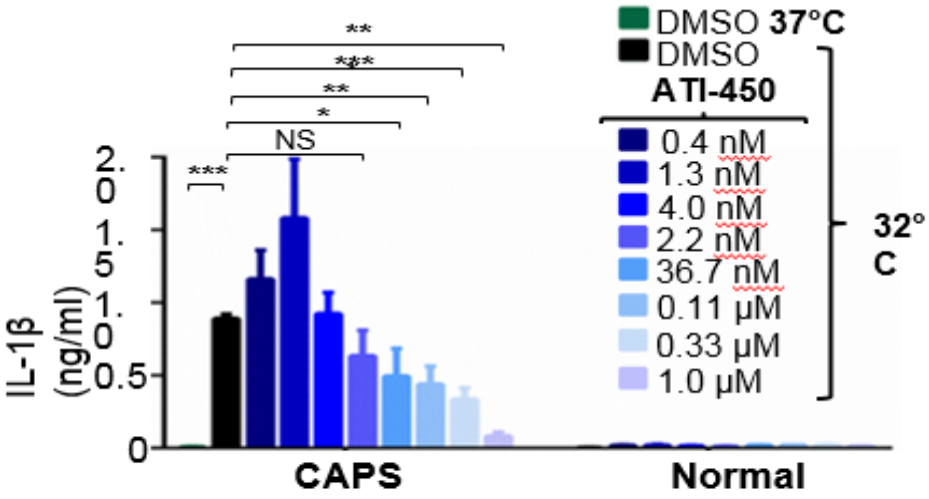


ATI-450 Efficacy in CAPS Auto-inflammatory Disease

Human CAPS Patient Blood and Murine CAPS Model

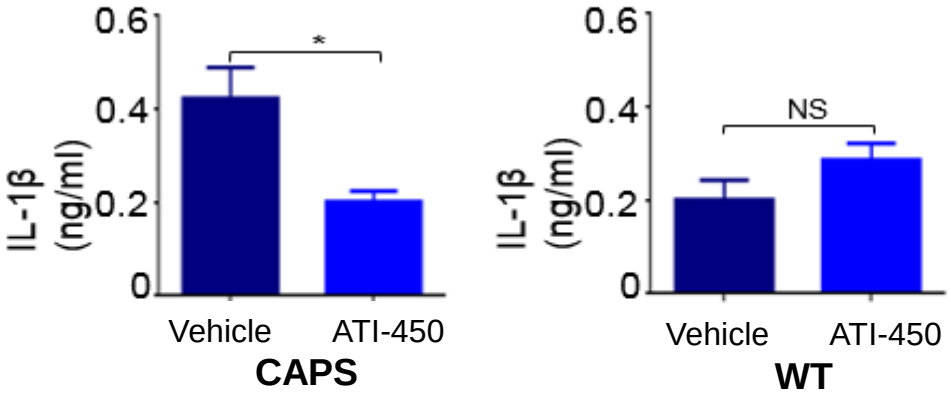
In human CAPS, ATI-450 inhibits:

- Low temperature-induced IL-1β in CAPS PBMCs
- Endotoxin-induced IL-1β in normal PBMCs



In CAPS mice, ATI-450 inhibits:

- IL-1β
- Leukocytosis/neutrophilia
- Thrombocytosis
- Lymphopenia
- Anemia



ATI-450 Drug Development Summary

Pharmacology

- Unprecedented pathway and kinome selectivity
- Low nM potency in enzyme, human cell and whole blood assays
- Differentiation from global inhibitor in cells and in vivo
- Robust activity in blocking cytokine production and arthritis in rats with oral dosing
- Active in blocking cytokine production and osteoclastogenesis in mouse model of human CAPS
- Emerging cancer application in combination with Chk1 kinase inhibitor

Safety

- Clean in hERG and gene tox assays
- Clean in CEREP broad pharmacology screen
- Rat 14-day and cynomolgus MTD completed

PK/ADME

- Good metabolic and plasma stability; low protein binding; highly cell permeable
- No CYP or transporter inhibition
- Good PK in mouse, rat, dog and cynomolgus leading to reasonable human dose projections

CMC

- API production in process

Issued Patents

- Covers candidate plus 8 other filings on backups

IND enabling studies initiated with submission target 18-24 months

ACLARIS THERAPEUTICS

Summary – MK2 Pathway Inhibitor ATI-450

- MK2PI mechanism has efficacy potential of anti-TNF and anti-IL1 biologics in an oral pill
- Broad scope of therapeutic indications in chronic inflammatory, autoimmune disease, auto-inflammatory disease, and cancer
- ATI-450 is a potent and selective development candidate with excellent oral drug-like properties
- IND-enabling studies are underway to support FIH studies within 18-24 months

ACLARIS THERAPEUTICS

THANK YOU

www.aclaristx.com