Finding New Ground Between Safety & Efficacy in Drug Development

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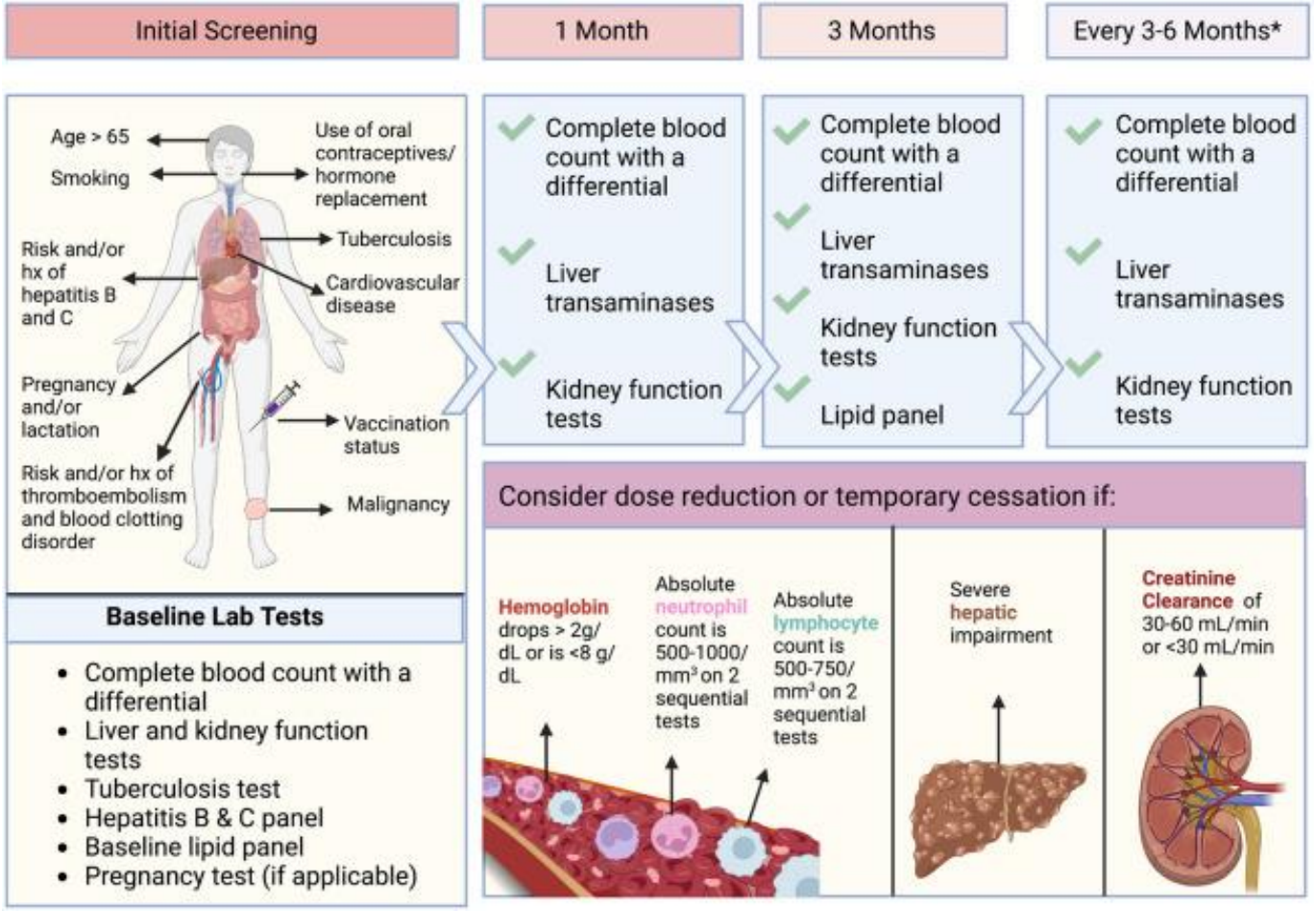
October 31, 2023

7th Dermatology Drug Development Summit

Unlocking New Therapeutic Possibilities

Regulatory Approved JAK Inhibitors Are Encumbered by Lab Monitoring and Safety Concerns



Samuel et al., Dermatol Ther (Heidelb). 2023 Mar;13(3):729-749

Goal to achieve impactful efficacy and avoid mechanisms known to drive safety signals to reduce clinical monitoring

Pharmacological Inhibition of the JAK Family Has Potential Broad Biological Consequences

Recludix Pharma

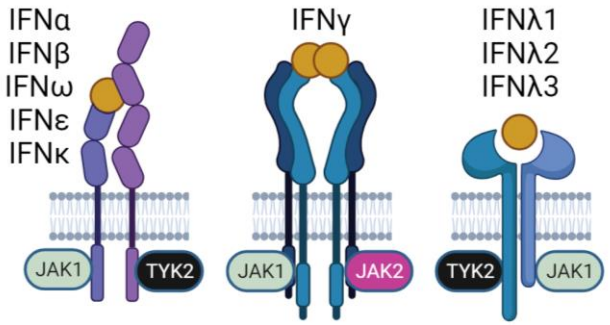
Biochemical IC_{50} at 1mM ATP

		JAK1	JAK2	JAK3	TYK2	Reference
JAK Inhibitors	Tofacitinib (pan JAK)	**15 nM**	77 nM	55 nM	489 nM	Clark et al., 2014
	Upadacitinib (JAK1)	**47 nM**	120 nM	2,304 nM	4,690 nM	Clark et al., 2014
	Abrocitinib (JAK1)	**29 nM**	803 nM	>15,000 nM	1,250 nM	Vazquez et al., 2018
	Ruxolitinib (JAK1/2)	**3.3 nM**	2.8 nM	428 nM	19 nM	Covington et al., 2020
	Baricitinib (JAK1/2)	**5.9 nM**	5.7 nM	>400 nM	53 nM	Covington et al., 2020
TYK2 Inhibitor	Deucravacitinib	>10,000 nM	>10,000 nM	>10,000 nM	**0.2 nM**	Wrobleski et al., 2019

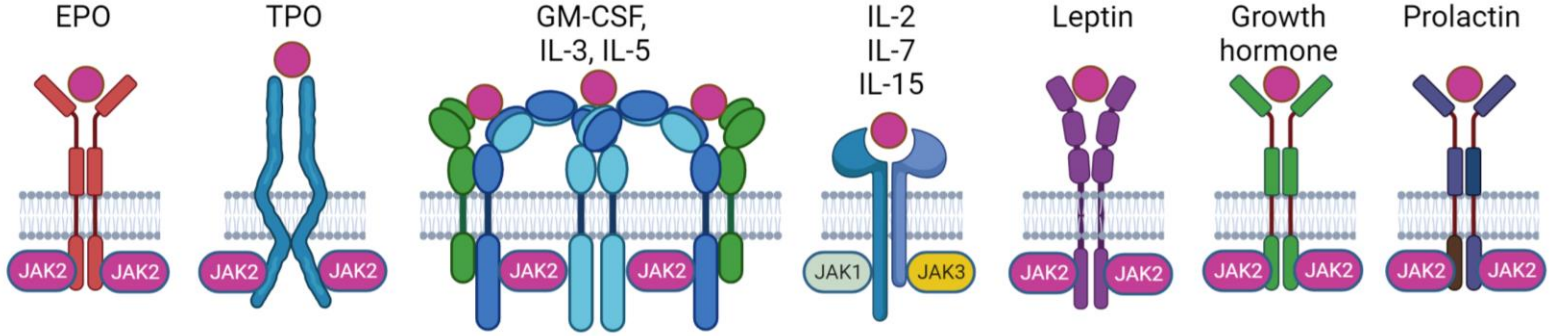
Selectivity relative to primary JAK family member:

- >30X
- 10-30X
- <10X

Anti-Viral Immunity



Hematologic Homeostasis & Development



Adapted from Morris et al., Protein Sci. 2018 Dec;27(12):1984-2009.

Unlocking Previously Intractable SH2 Domains of High Value Targets in Inflammatory Diseases and Cancer

Recludix Pharma

Platform Company

Experienced Team Drives Success

Recludix-created platform integrates custom designed DEL libraries, massively parallel SAR, and proprietary screening tools

Fuels the pipeline with 5 selected targets

Oral STAT3

Wholly-Owned Program

Potential applications across Th17 driven diseases, including psoriasis, RA, IBD, and multiple oncology indications

Validated by JAK/TYK2i with potential for greater efficacy and less toxicity

IND 2024

Oral STAT6

Global Partnership

sanofi

Inhibition of STAT6 with oral small molecule represents an attractive alternative to biologics in targeting Th2 driven diseases

Validated by IL-4 and IL-13 biologics

IND 2025

Pipeline

Inflammation & Precision Oncology

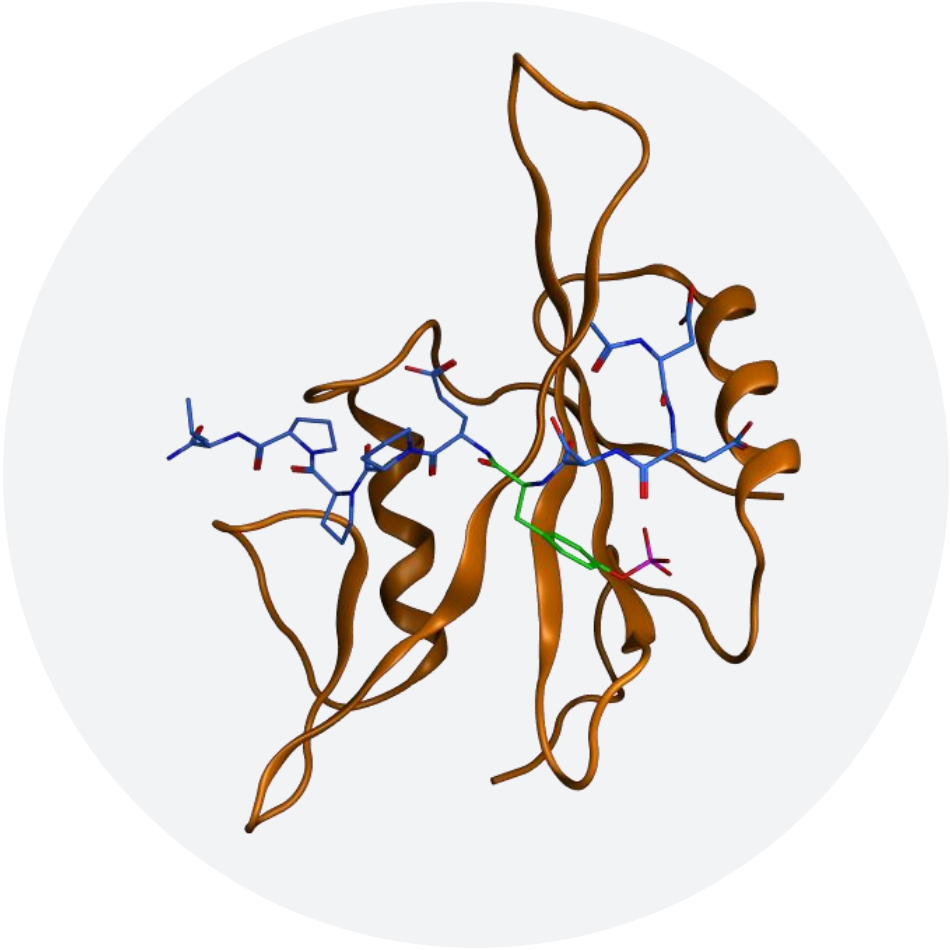
Opportunities in therapeutically validated pathways where selective, oral agents would provide competitive advantage

Additional pipeline and partnering opportunities

SH2 Domains Have Previously Been Deemed “Undruggable”

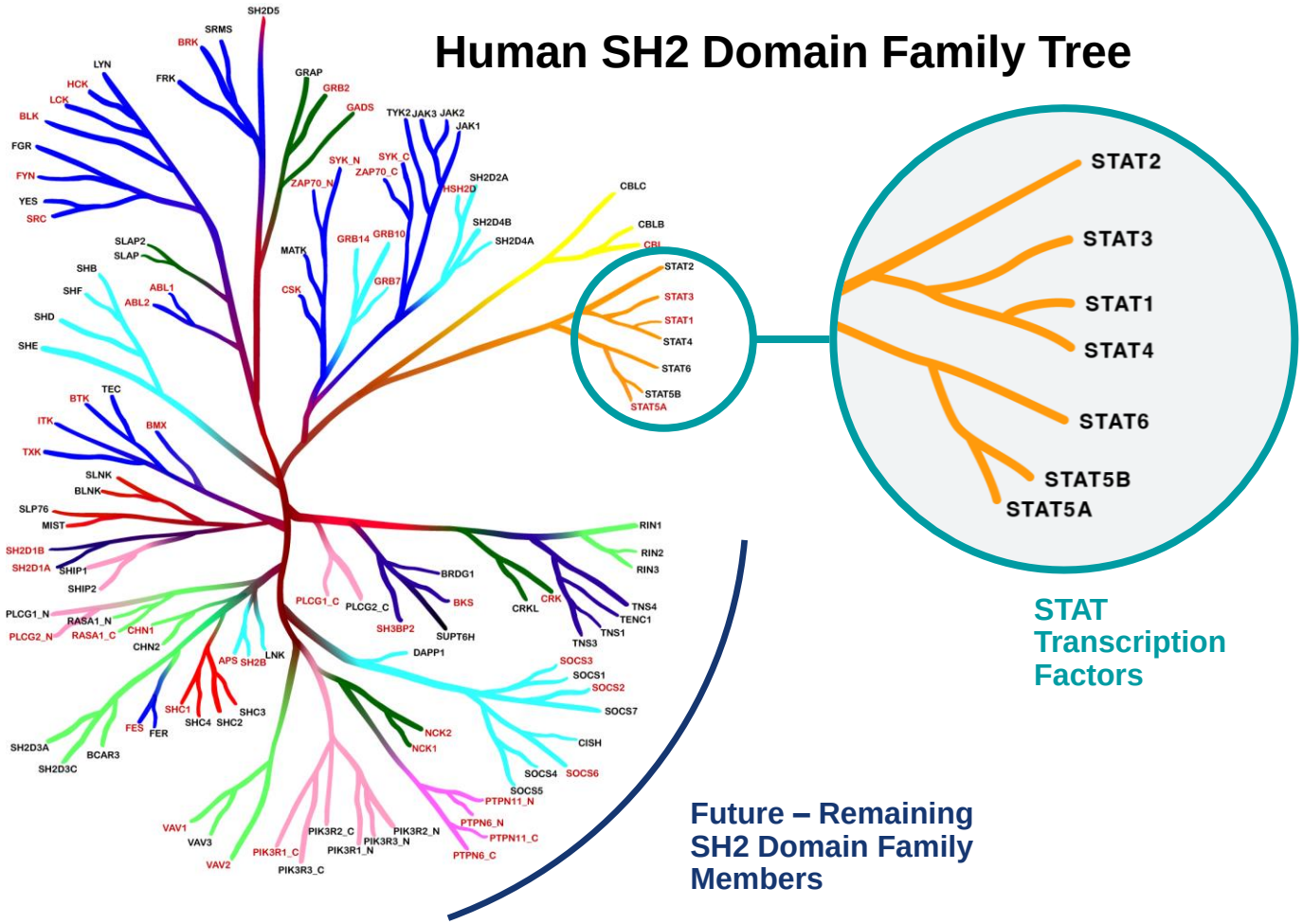
Src Homology 2 (SH2) domains are highly conserved protein domains that have long been recognized as attractive drug targets

- Small protein modules made up of ~100 amino acids
- 120 human SH2 domains
- Play a key role in regulating the location and activity of proteins and in cellular signal transduction
- Mediate protein-protein interactions by binding to phospho-tyrosine containing motifs



Significant Opportunity in Targeting SH2 Domain Proteins

Initially Focused on STAT3, STAT6 and 3 Additional Targets



1. STAT Transcription Factors

- Strong biological validation for STAT3 and STAT6
- Downstream in the JAK/STAT pathway; selective STAT inhibitors likely to be more targeted with fewer side effects

2. Undisclosed

- Plays a central role in both cancer and autoimmune diseases

3. Future - Remaining SH2 Domain Family Members

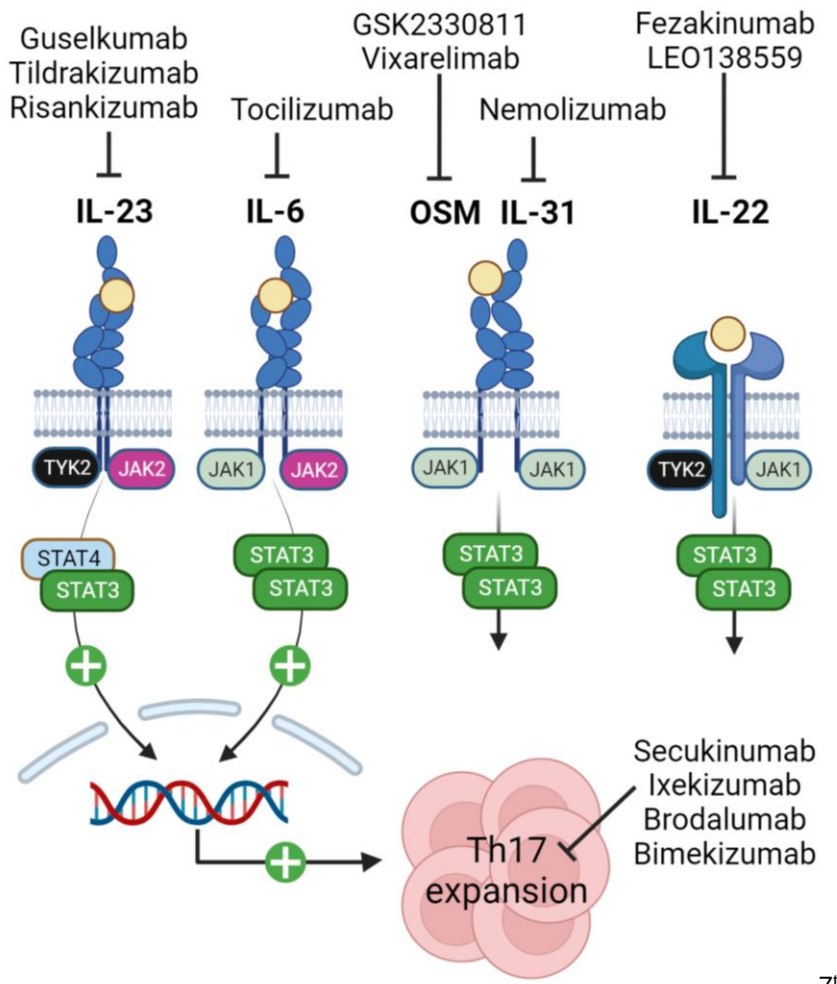
- Additional compelling targets enable a sustainable pipeline

Adapted from Liu et al., Mol Cell. 2006 Jun 23;22(6):851-868.

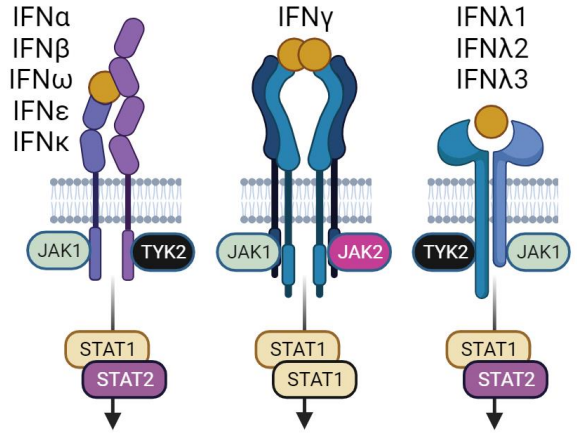
Selective STAT3 Inhibition Targets Key Inflammatory Cytokines and Downstream Th17 Pathogenesis

JAK/TYK2 inhibitors impact mechanisms important for viral immunity and hematologic homeostasis

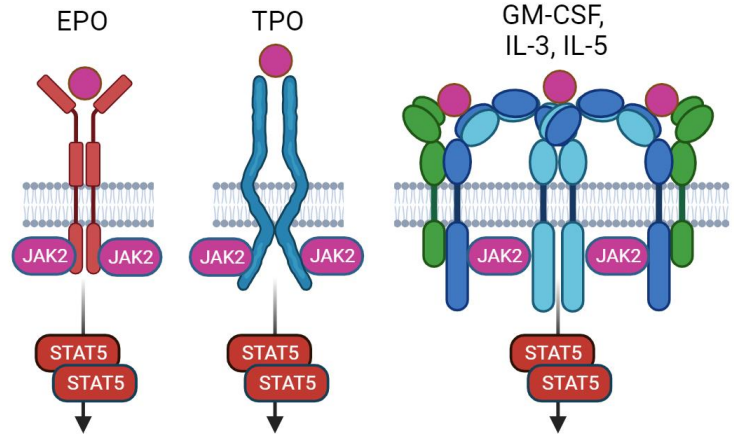
Pro-inflammatory cytokines



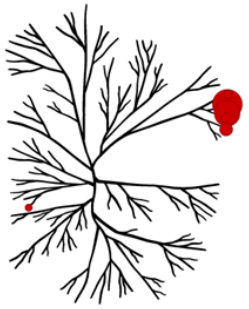
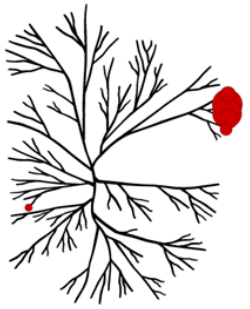
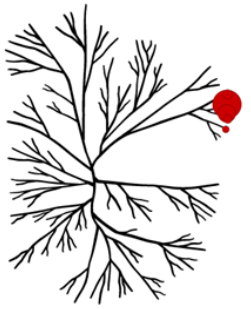
Anti-Viral Immunity



Hematologic Homeostasis



Recludix Has Identified Multiple Highly Potent and Selective STAT3 Inhibitors

	in vivo i.p. tool	*orally bioavailable compounds*	
	REX-4019	**REX-5376**	**REX-7117**
Biochemical Potency (SH2scan K_D)	0.28 nM	0.15 nM	0.16 nM
Cellular Potency (pSTAT3 IC_{50} in human PBMCs)	5.1 nM	0.72 nM	1.2 nM
Biochemical STAT Family Selectivity	~15X vs. STAT1 >300X vs. STAT2/4/5/6	~2X vs. STAT1 >150X vs. STAT2/4/5/6	~20X vs. STAT1 >500X vs. STAT2/4/5/6
Cellular Selectivity (PBMCs)	>10X vs. STAT1 >100X vs. STAT2/4/5/6	~2X vs. STAT1 ~20X vs. STAT2 >300X vs. STAT4/5/6	~20X vs. STAT1 >500X vs. STAT2/4/5/6
SH2 Domain Selectivity			

STAT3 Inhibition Impairs the Th17 Phenotype and Differentiates From JAK/TYK2 Inhibitors in Functional T Cell Assays

- Primary human T cells cultured under Thelper (Th) skewing conditions in the presence of compounds

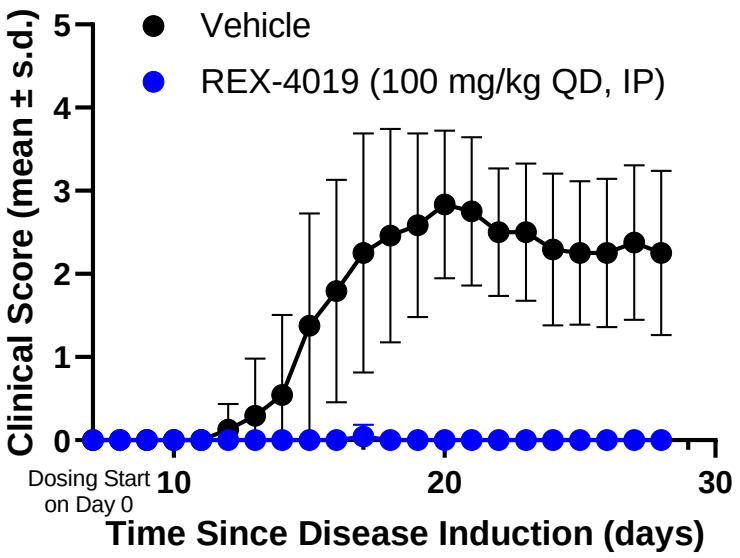
		T cell function assays (IC_{50})			
		General Adaptive Immune response	Defense against viruses and bacteria	Defense against extracellular pathogens	Defense against parasites and mediation of antibody responses
		T Cell Activation (CD25)	Th1 Cell Function (IFNγ)	Th17 Cell Function (IL-17A)	Th2 Cell Function (IL-5)
STAT3 Inhibitors	REX-4019	>10,000 nM	>2,000 nM	48 nM	>3,000 nM
	REX-5376	>10,000 nM	>2,000 nM	11 nM	>3,000 nM
	REX-7117	>10,000 nM	>2,000 nM	14 nM	>3,000 nM
TYK2 Inhibitor	Deucravacitinib	>3,000 nM	260 nM	34 nM	~3,300 nM
JAK Inhibitors	Tofacitinib	340 nM	74 nM	20 nM	20 nM
	Upadacitinib	39 nM	36 nM	8 nM	4.4 nM
	Baricitinib	110 nM	210 nM	15 nM	15 nM

Selectivity relative to Th17 inhibition: >30X 10-30X <10X

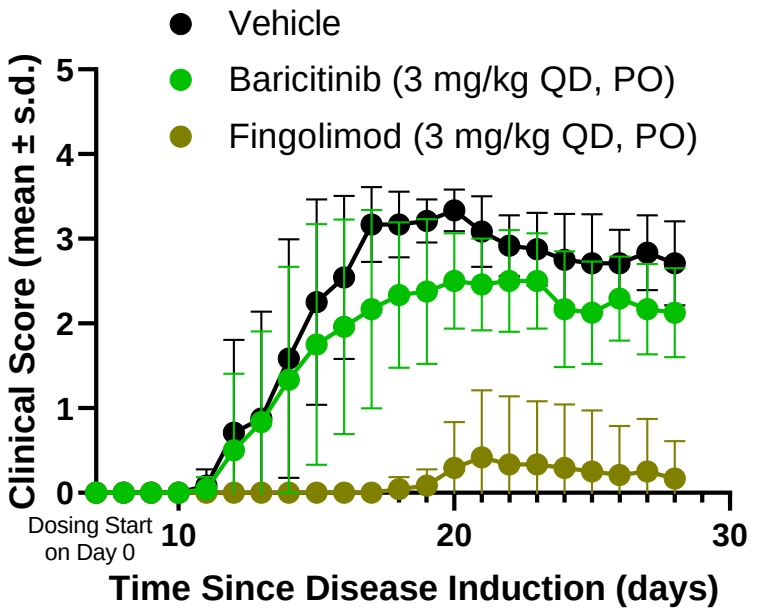
Proof-of-Concept That Reversible Small Molecule STAT3 Inhibition Modulates In Vivo Th17 Disease

- Initial published characterization of Th17 cells was in the mouse EAE model
- Conditional STAT3 knockout mice are completely resistant to EAE induction

Recludix Compound



Benchmark Compounds



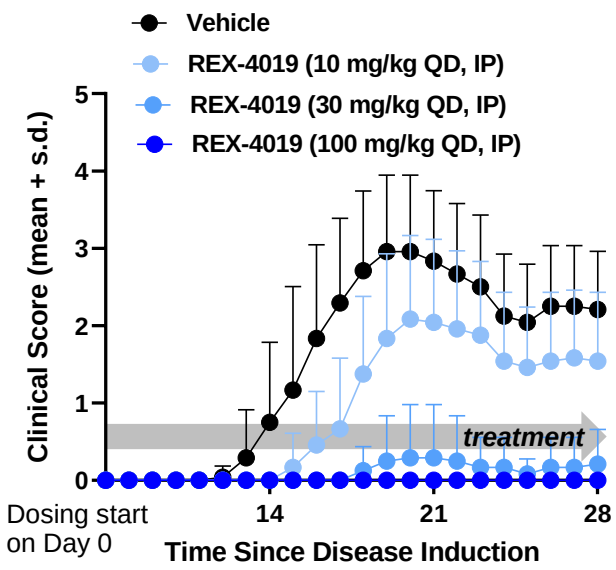
REX-4019 is active in mouse experimental autoimmune encephalomyelitis (EAE)

Chen et al., J Clin Invest. 2006 May;116(5):1317-26.
Komiyama et al., J Immunol. 2006 Jul 1;177(1):566-73
Zhou et al., Bone. 2011;49:404

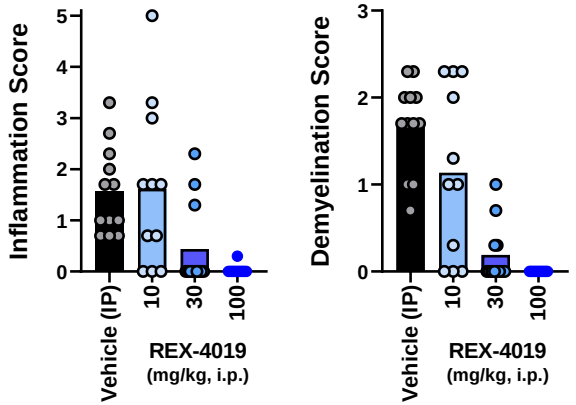
Prophylactic and Therapeutic Dose-Dependent Efficacy in the Th17-Dependent EAE Model

Prophylactic

Neurological symptoms

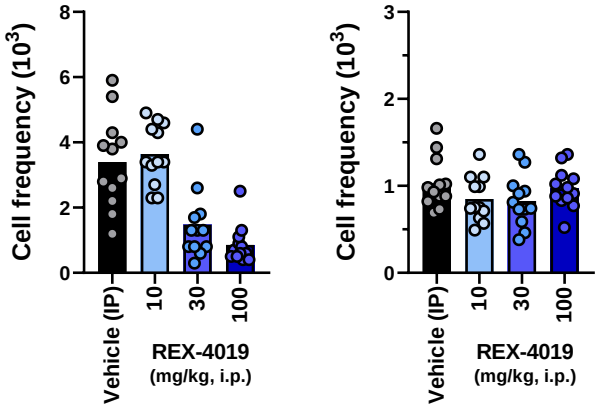


CNS tissue pathology

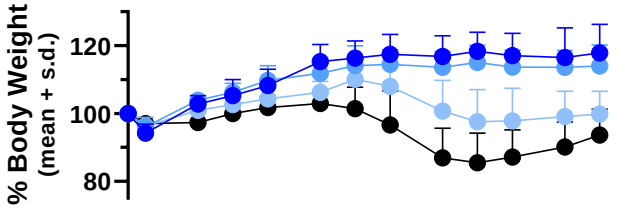


CNS Infiltrating Th17 cells

Peripheral Treg cells

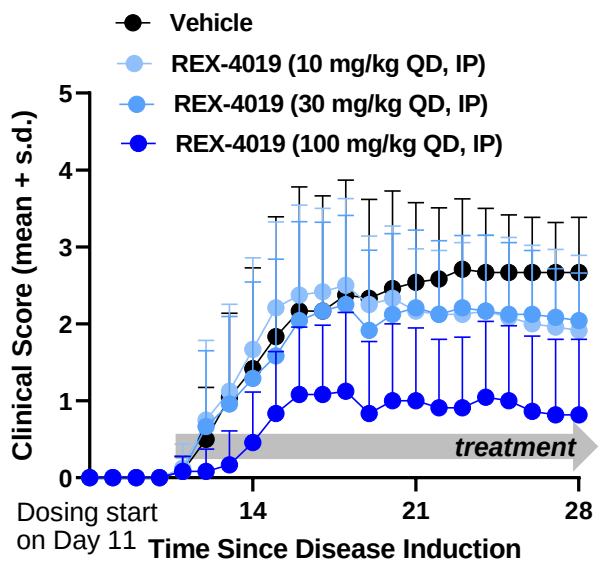


Inflammation-induced cachexia

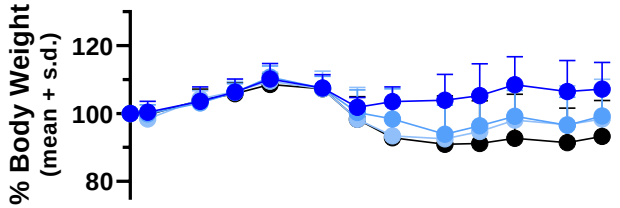


Semi-Therapeutic

Neurological symptoms

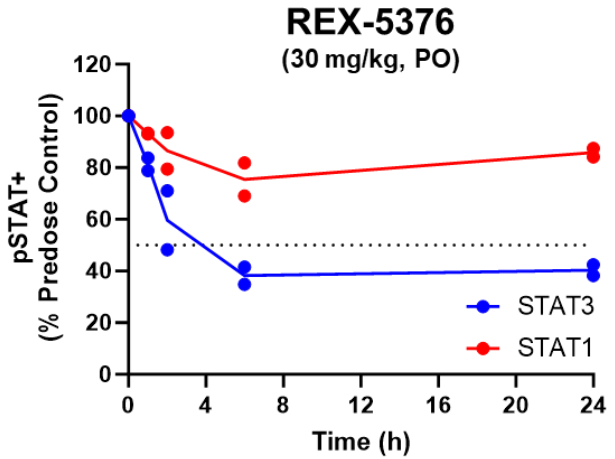


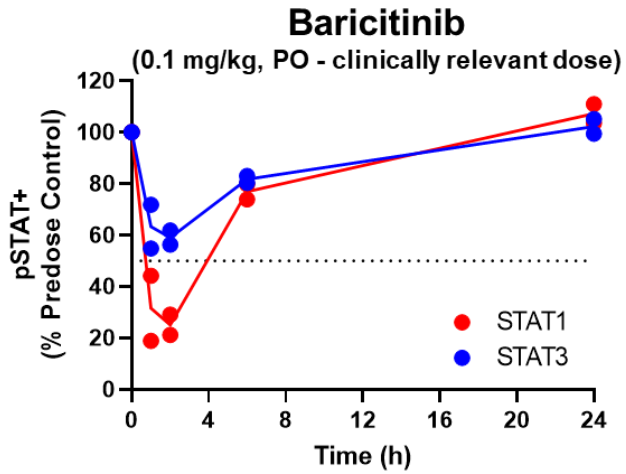
Inflammation-induced cachexia

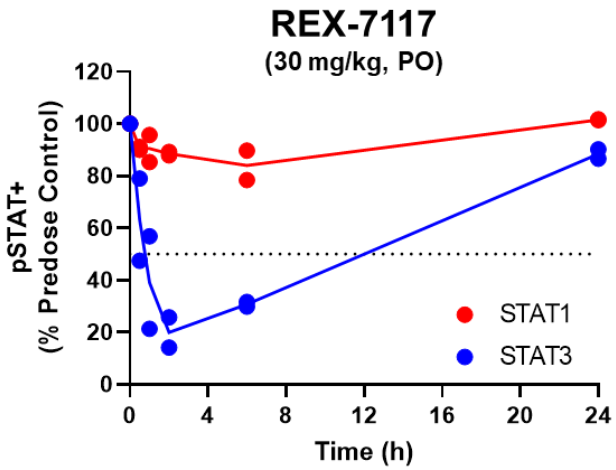


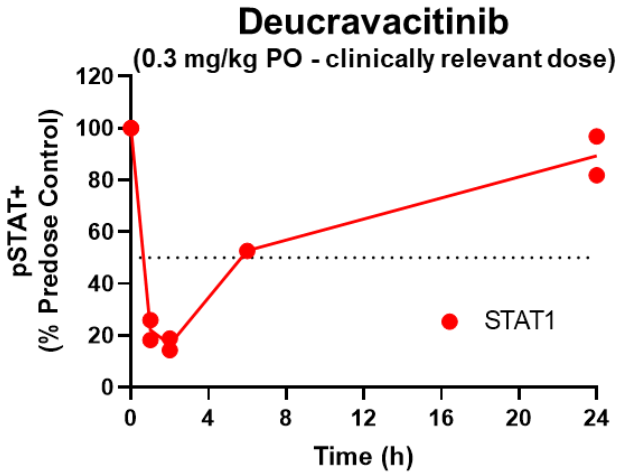
Recludix Oral STAT3 Compounds Characterized by Selective and Sustained Target Inhibition

- Dog PBMCs evaluated for *ex vivo* pSTAT1/3 activity following single day oral dosing





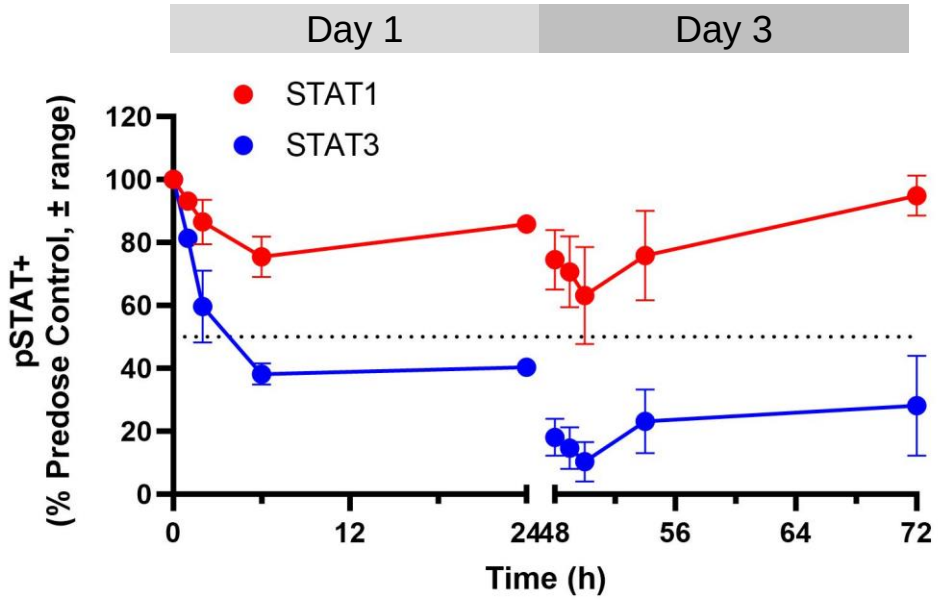




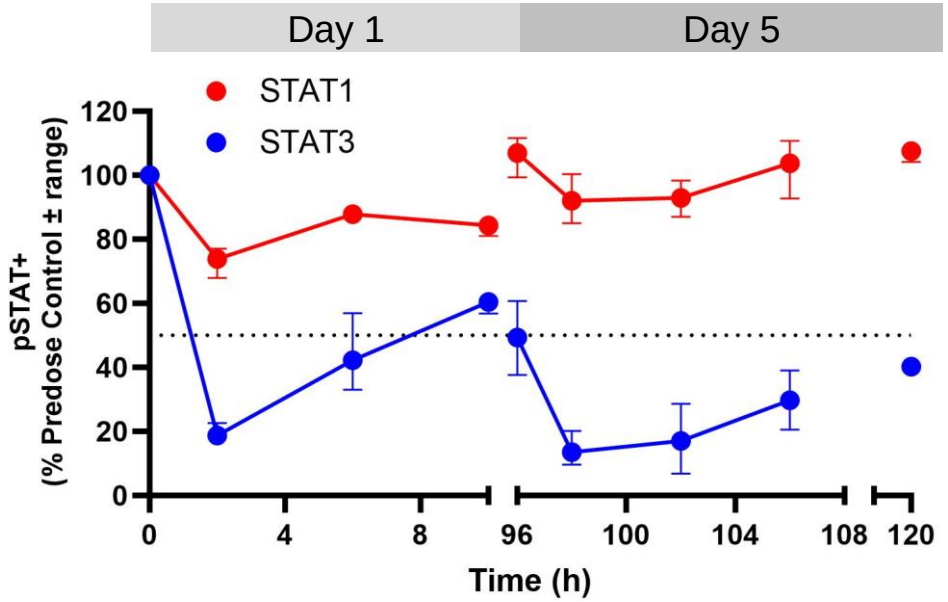
Recludix Compounds Provide Durable STAT3 Inhibition and Maintain In Vivo Selectivity Versus STAT1 After Multiple Doses

- Dog PBMCs evaluated for *ex vivo* pSTAT1/3 activity following multi-day oral dosing

REX-5376
(30 mg/kg, PO, QD)



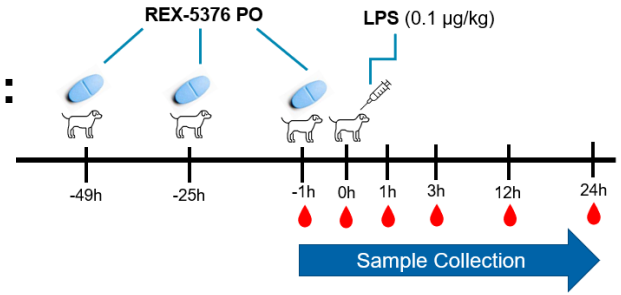
REX-7117
(30 mg/kg, PO, BID)



Repeat oral dosing confirms that *in vivo* STAT3 selectivity is achievable against the closest off-target family member

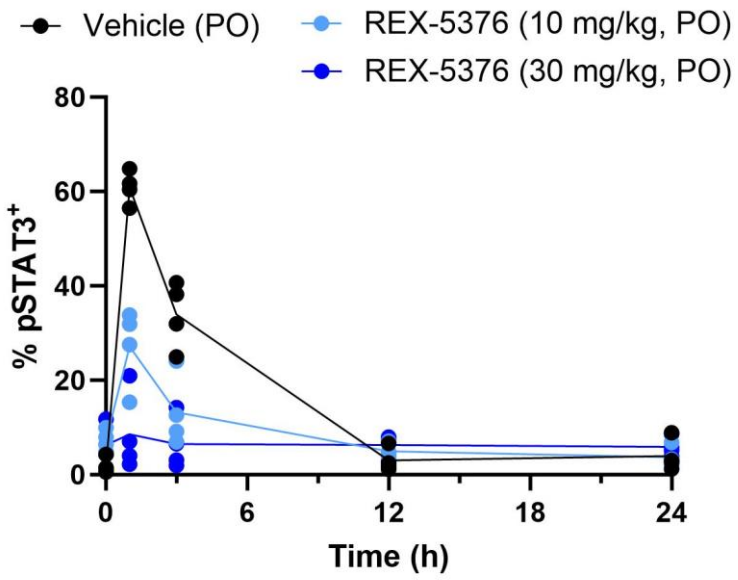
Oral STAT3 Inhibition Significantly Reduces an IL-6 Dependent LPS-Induced Inflammation in Dogs

Study Design:

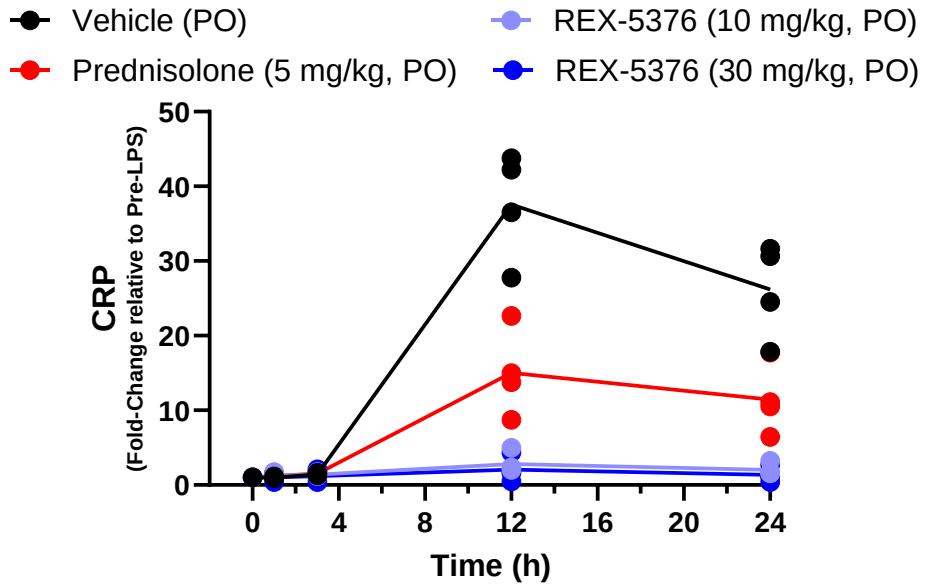


- LPS challenge drives pSTAT3 activation, immune activation, and IL-6 dependent CRP production
- Oral REX-5376 inhibits endogenous pSTAT3 signaling and abrogates CRP induction

PBMC pSTAT Activity



Serum CRP

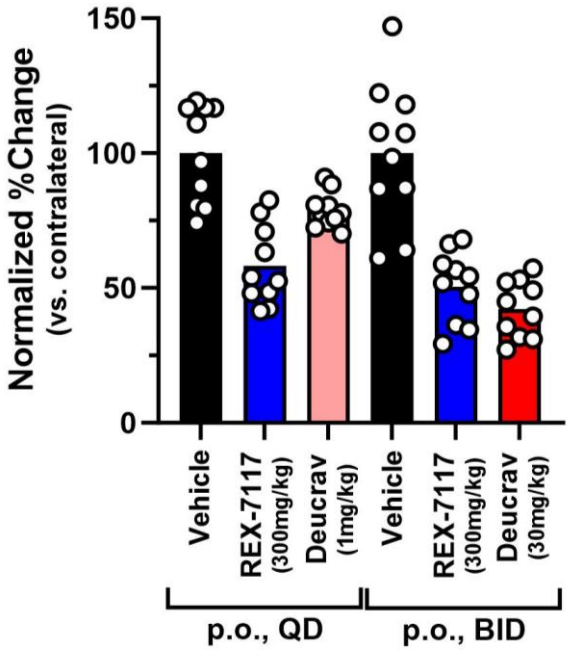


Oral STAT3 inhibition effectively impairs IL-6 mediated inflammatory responses

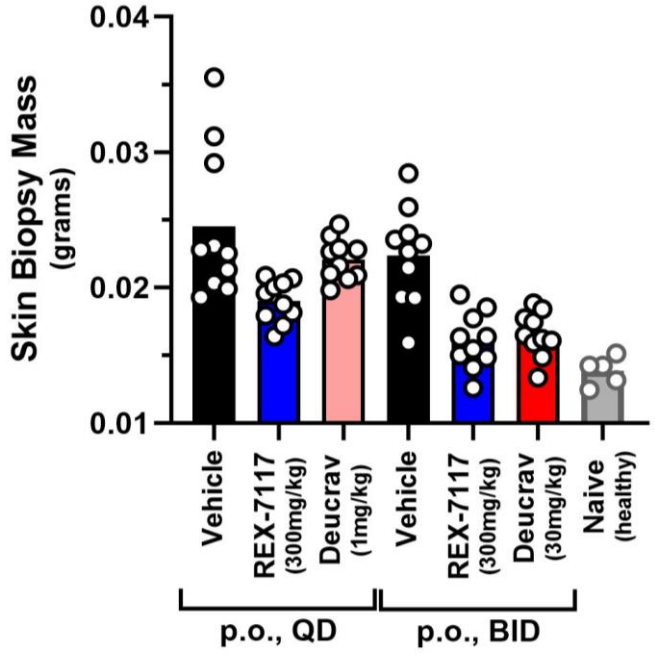
REX-7117 Is Efficacious After Oral Dosing in IL-23-Induced Th17 Model of Psoriasis

- Rodent doses selected to mimic expected human pSTAT3 pharmacodynamic profile
- Once daily REX-7117 (300mg/kg) was superior to deucravacitinib clinically-relevant dose (1mg/kg)
- Twice daily REX-7117 (300mg/kg) was comparable to deucravacitinib at a supra-clinical dose (30mg/kg)

Tissue Inflammation



Tissue Weight

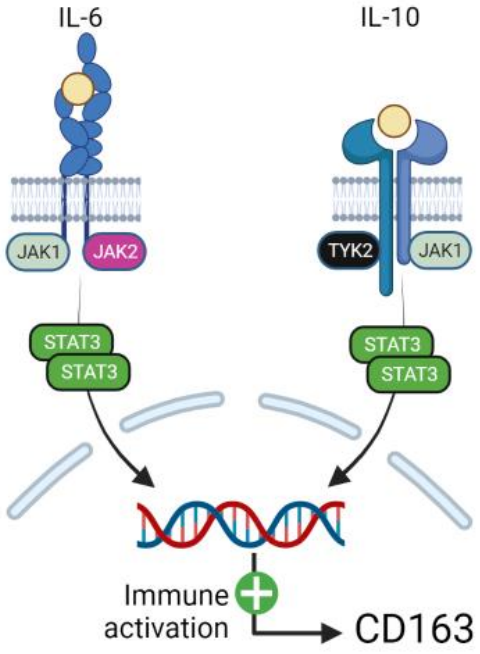


Orally targeting STAT3 provides significant inhibition of Th17 mediated skin inflammation

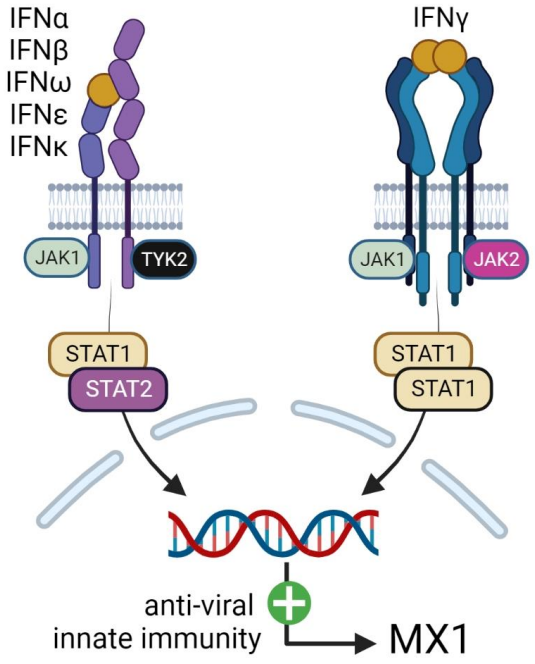
Selective STAT3 Inhibition Relatively Spares Interferon-Driven Anti-Viral Gene Transcription

- Benchmarking selective STAT3 inhibition to clinically relevant JAK/TYK2 therapies using interferon (IFN) response gene in primary human monocytes

STAT3 signaling



Anti-Viral Immunity



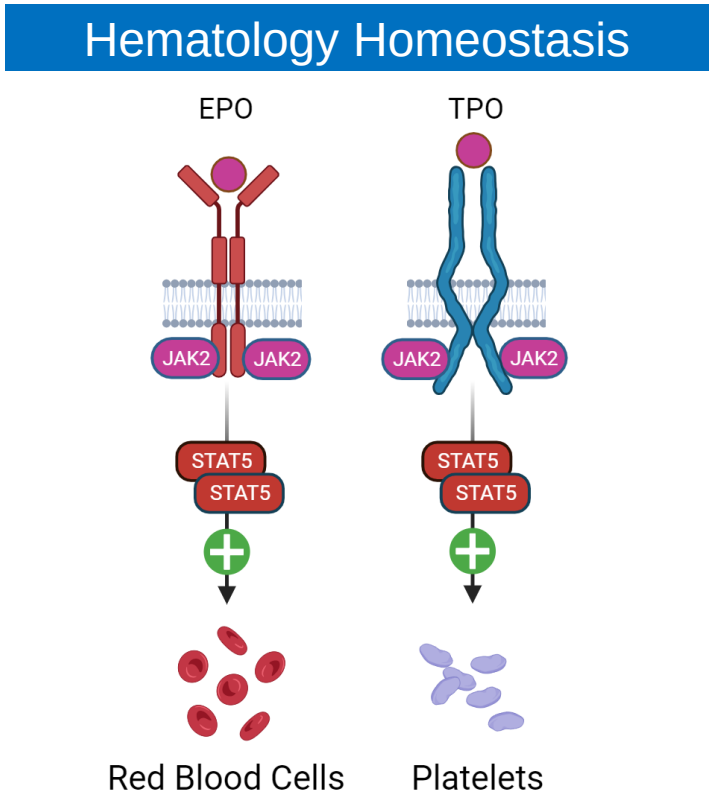
		STAT3-driven Inflammation	STAT1/2-driven Anti-Viral Response	
		IL-6 + IL-10 Response in Monocytes (CD163)	IFNβ Response in Monocytes (MX1)	IFNγ Response in Monocytes (MX1)
STAT3 Inhibitors	REX-4019	2.01 nM	960 nM	330 nM
	REX-5376	0.43 nM	7.2 nM	3.9 nM
	REX-7117	0.13 nM	17 nM	2.8 nM
TYK2 Inhibitor	Deucravacitinib	31 nM	38 nM	570 nM
JAK Inhibitors	Tofacitinib	103 nM	1,400 nM	55 nM
	Upadacitinib	43 nM	130 nM	6.7 nM
	Baricitinib	370 nM	280 nM	9.7 nM

Selectivity relative to monocyte CD163 inhibition: >30X 10-30X <10X

Targeting STAT3 will reduce the impact on IFN-dependent innate immunity

Targeting STAT3 Differentiates From Clinically Relevant JAK Inhibitors on pSTAT5 Mediated Signaling

- Profiling compounds on Erythropoietin (EPO) or Thrombopoietin (TPO) mediated pSTAT5 signaling in reporter cell lines

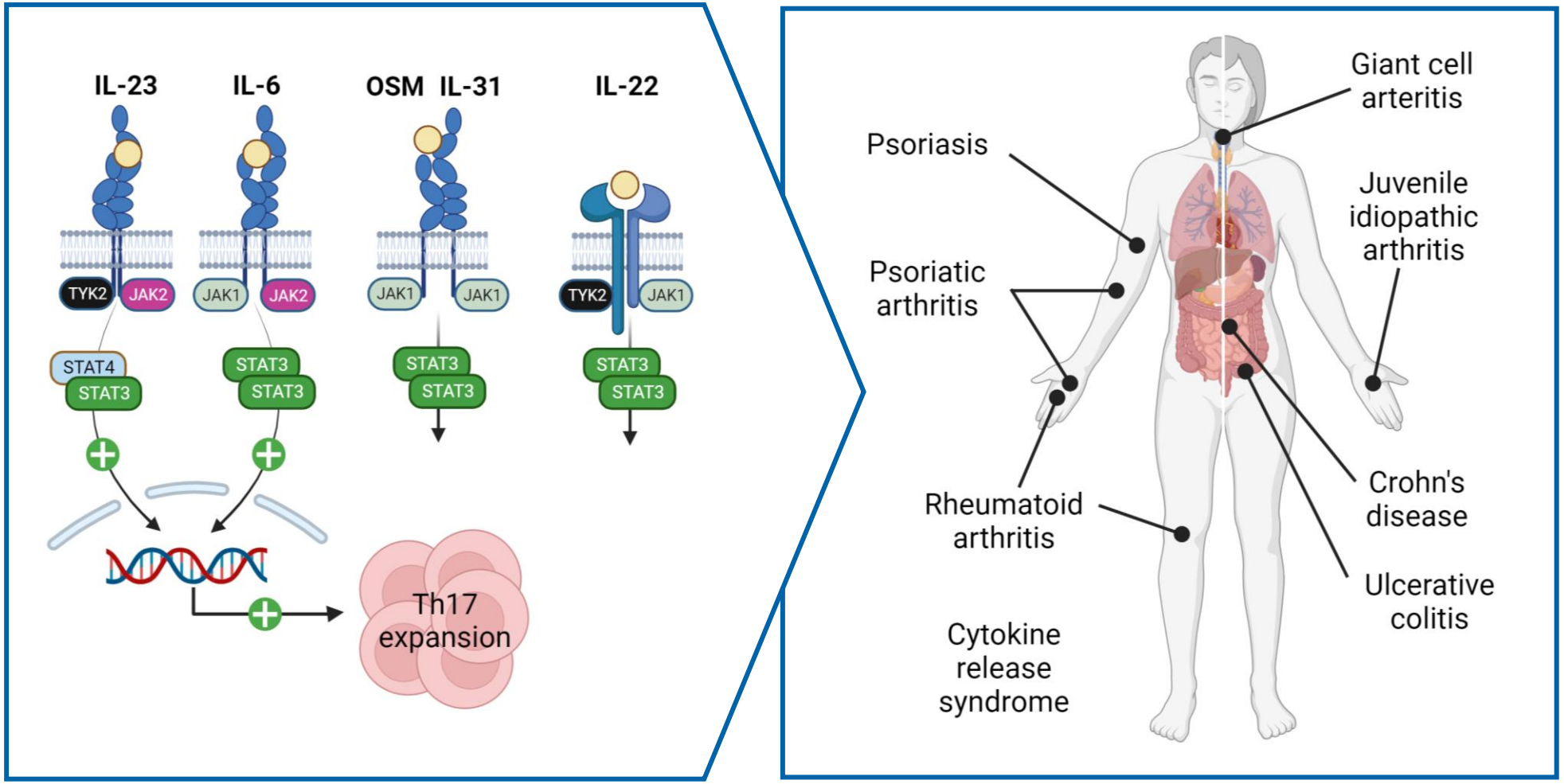


		STAT3-driven Inflammation	Erythropoiesis	Thrombopoiesis
		IL-6 STAT3 in PBMCs	EPO-Induced STAT5-Driven Transcription	TPO-Induced STAT5-Driven Transcription
STAT3 Inhibitors	REX-4019	5.1 nM	>10,000 nM	>10,000 nM
	REX-5376	5.6 nM	>10,000 nM	>10,000 nM
	REX-7117	0.9 nM	>10,000 nM	>10,000 nM
TYK2 Inhibitor	Deucravacitinib	140 nM	3,200 nM	250 nM
JAK Inhibitors	Tofacitinib	110 nM	340 nM	200 nM
	Upadacitinib	48 nM	69 nM	20 nM
	Baricitinib	28 nM	55 nM	46 nM

Selectivity relative to PBMC pSTAT3 inhibition: >30X 10-30X <10X

Targeting STAT3 is expected to avoid STAT5 signaling that is important for hematologic homeostasis

STAT3 Inhibition Has Potential Clinical Applications Across Multiple Inflammatory and Autoimmune Diseases



Leveraging clinically validated mechanisms with selective STAT3 inhibition

Recludix's Reversible, Oral, Small Molecule STAT Inhibitors Are Differentiated From Competitors

	Recludix's STAT Inhibitors	TYK2 Inhibitors	JAK Inhibitors	Biologics
Potent	+++	+++	+++	++++
Selective	++++	++	+	++++
Reversible	++++	++++	++++	+
Oral	++++	++++	++++	-
Indication Expansion Potential	++++	++	++++	++++

Oral, Selective, STAT Inhibitors Offer Potential New Ground Between Safety & Efficacy in Drug Development

- Recludix has generated potent and selective small molecule STAT3 inhibitors for Th17 driven inflammation
- Exquisite STAT3 targeting has the potential for both efficacy and safety differentiation versus the JAK/TYK family
- STAT3 inhibition has potential clinical applications across Th17 driven diseases, including psoriasis, RA, IBD, and multiple oncology indications
- Integrated platform technologies facilitate drugging of previously ‘undruggable’ targets, including other STAT family members

Thank you

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Unlocking New Therapeutic Possibilities