Drugging the Undruggable

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Rĕclūdo (Latin)
transitive verb III conjugation
1 to open
2 to open up, to disclose, to reveal, to unlock

Unlocking New Therapeutic Possibilities

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

Broad immunology and oncology pipeline

Target	Program	Discovery	Lead Optimization	IND-Enabling	Partner
STAT3 SH2 domain	Inflammatory Diseases				Wholly-owned
	Cancer				
STAT6 SH2 domain	Inflammatory Diseases				sanofi[1]
	Cancer				
Undisclosed SH2 domain	Inflammatory Diseases				Wholly-owned
	Cancer				
Undisclosed SH2 domain	Cancer				Wholly-owned
Undisclosed Non-SH2 domain	Cancer				Wholly-owned

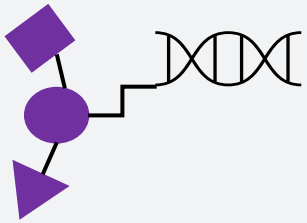
[1]Option to participate in an equal profit-sharing arrangement in the US, which includes certain co-promotion activities

Recludix Platform: Integrated proprietary technologies & new chemical approaches

Recludix Pharma

Discovery and SAR DELs

Millions of molecules



Custom DNA Encoded Libraries

Unique assay panel of SH2 domains

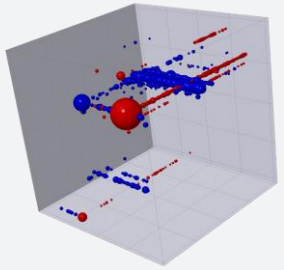
Drives selectivity

SH2 Domain Screening Tool

High Quality Lead Compounds

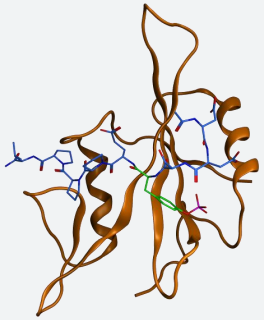
Proprietary DEL Selection & SAR Analysis

Rapid, massively parallel resolution of structure-activity relationships



Structure-Based Design

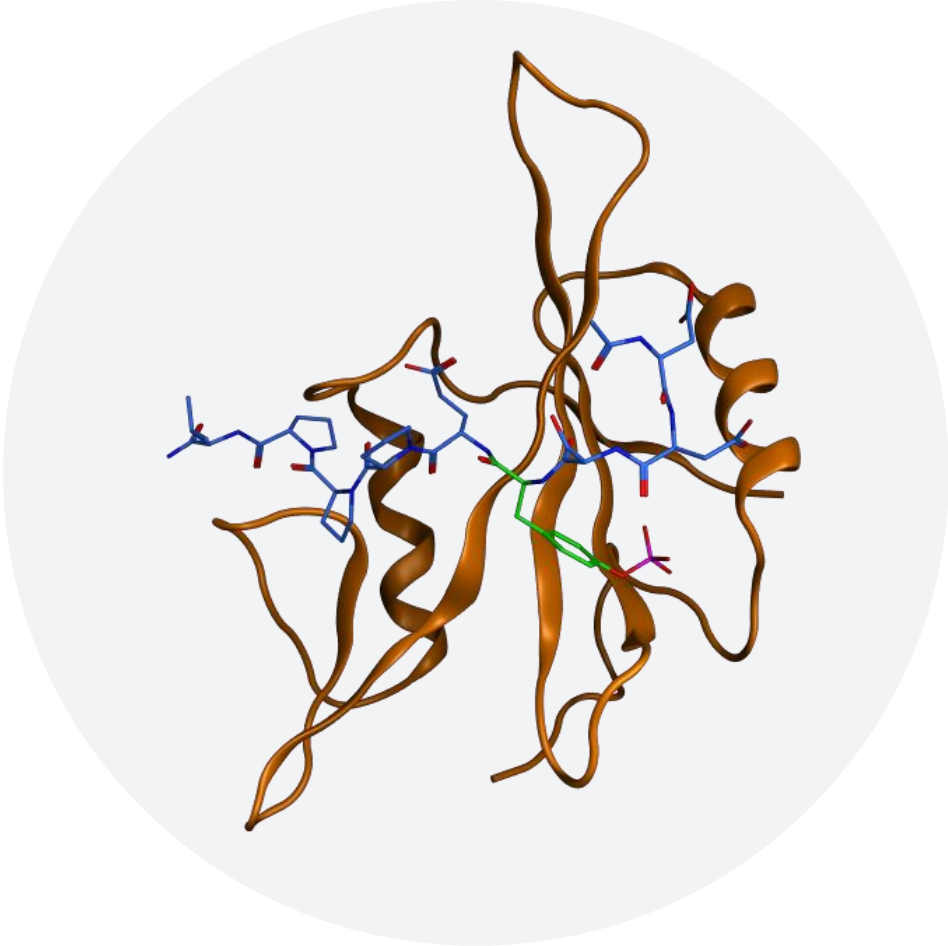
Proprietary co-crystallography systems



SH2 domains have previously been deemed “Undruggable”

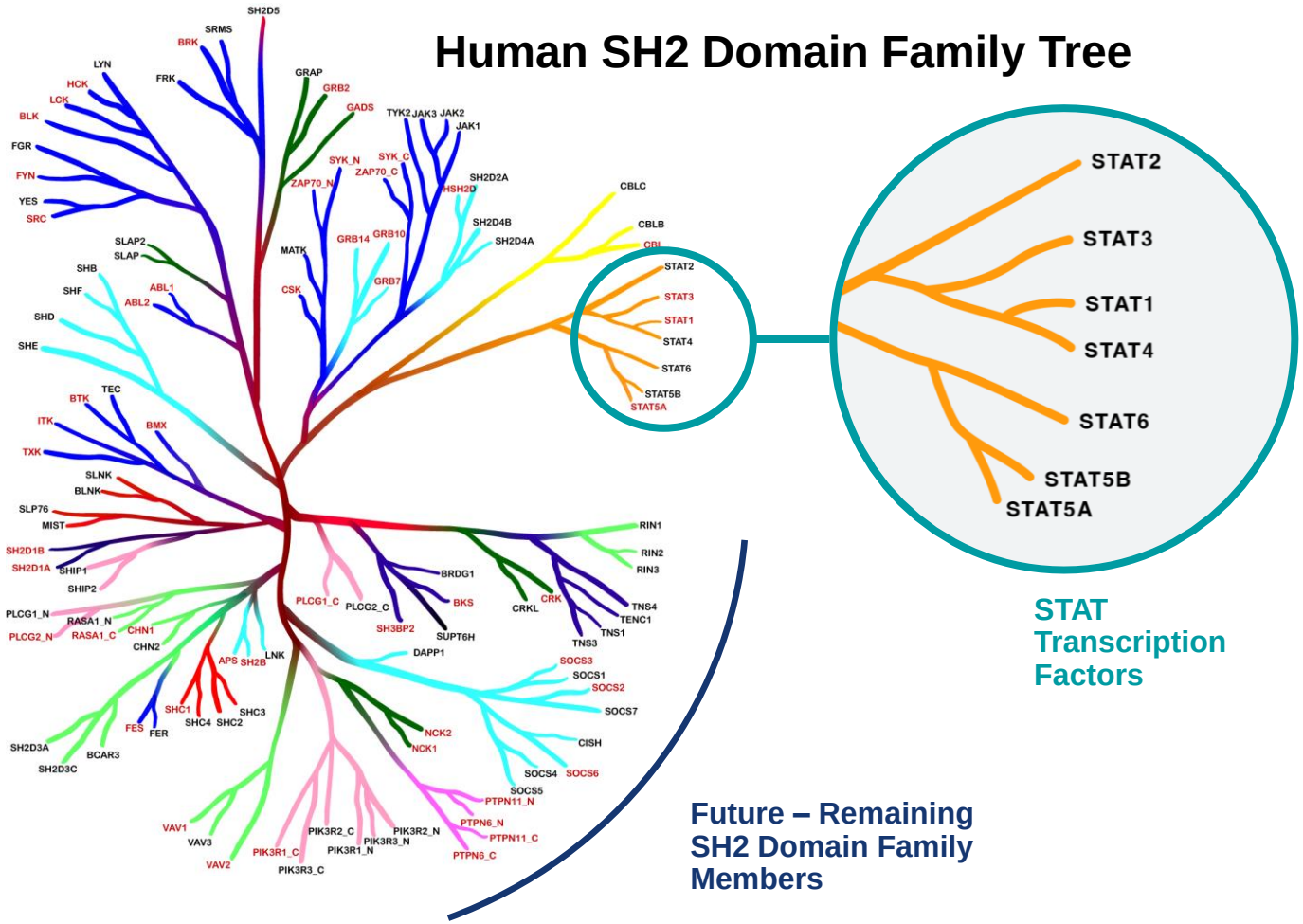
Src Homology 2 (SH2) domains are highly conserved protein domains that have long been recognized as attractive drug targets

- 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

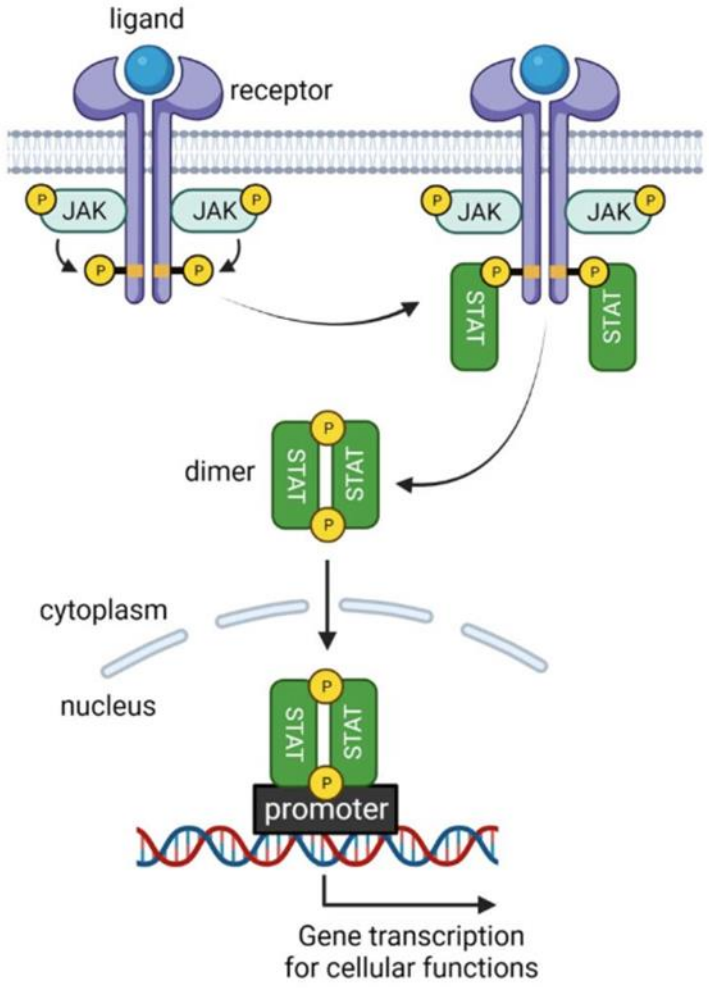
Adapted from Liu et al., Mol Cell. 2006 Jun 23;22(6):851-868.

STAT transcription factors drive immune system and oncogenic signaling

STAT proteins have been challenging to drug over the past 20 years but are yielding to Recludix's approach

The JAK/STAT pathway drives inflammatory diseases and cancer:

- In inflammatory diseases:
  - Required for function of disease-driving T cell populations
- In cancer:
  - Gain-of-function mutations
  - Aberrant upstream activation of the pathway
  - Mediates immunosuppressive tumor microenvironment

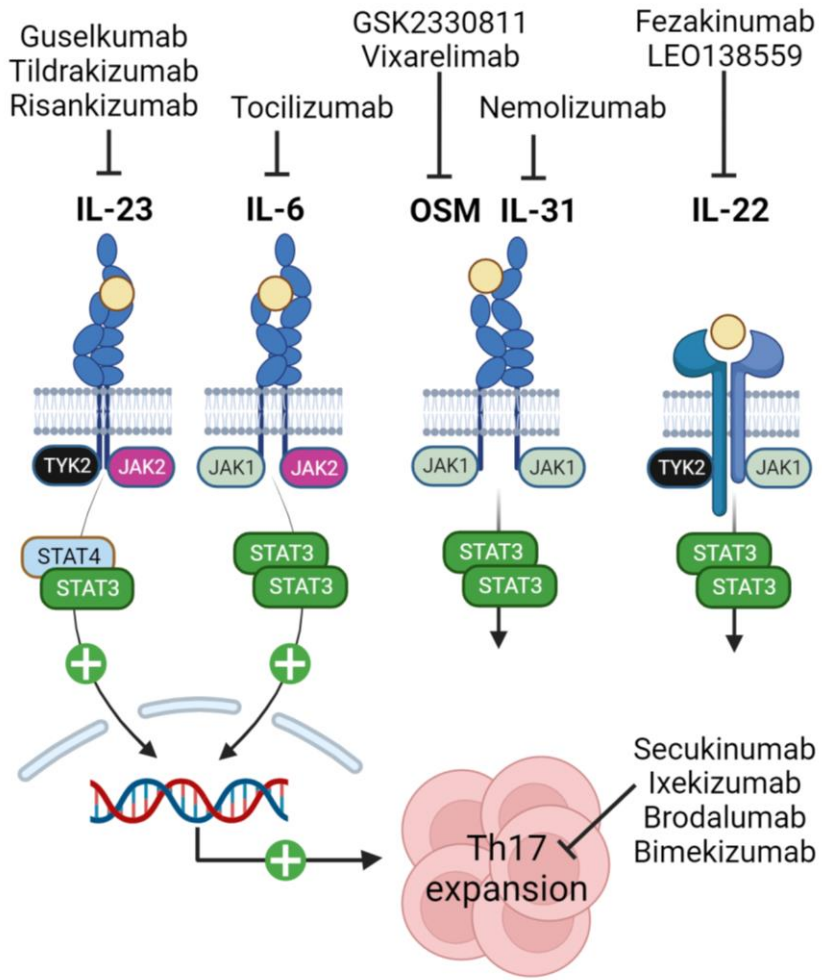


Adapted from Miklossy et al., Nat Rev Drug Discov 2013 Aug;12(8):611-29.

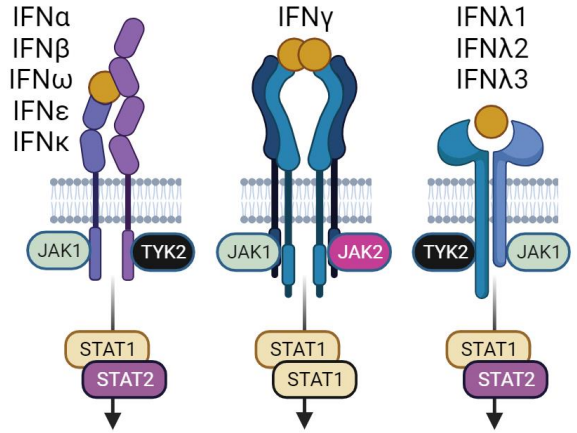
Selective STAT3 inhibition targets key inflammatory cytokines and downstream Th17 pathogenesis

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

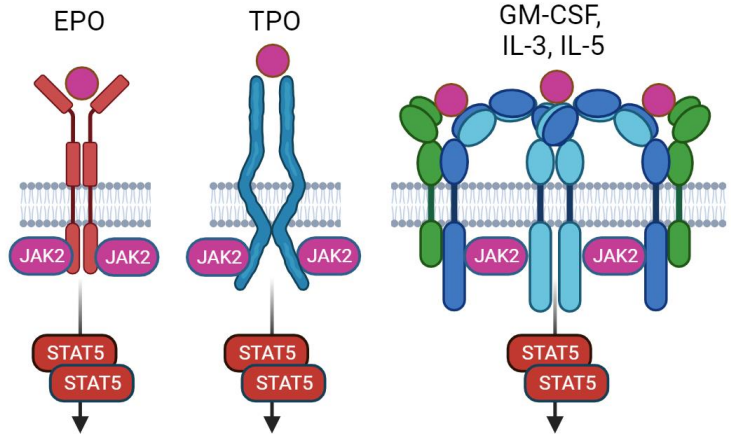
Pro-inflammatory cytokines



Anti-Viral Immunity



Hematologic Homeostasis



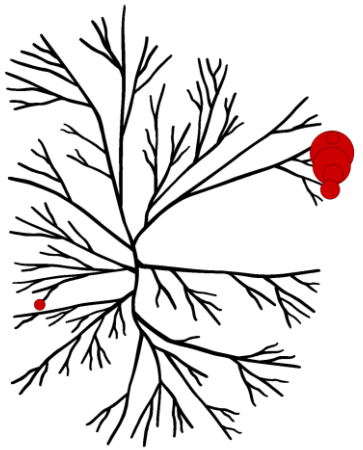
Recludix's reversible, oral, small molecule STAT inhibitors are differentiated from competitors

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

STAT3

Reversible STAT3 inhibitor *in vivo* tool compound is potent and selective in biochemical and cellular assays

REX-4019

Biochemical Potency (SH2scan K_D)	Cellular Potency (pSTAT3 IC_{50} in human PBMCs)	Biochemical STAT Family Selectivity	Cellular Selectivity (PBMCs)	SH2 Domain Selectivity
0.28 nM	6.1 nM	~15X vs. STAT1 >300X vs. STAT2/4/5/6	>30X vs. STAT1 >100X vs. STAT2/4/5/6	

Selective STAT3 inhibitors are differentiated from JAK 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			
		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**
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	**8.0 nM**	4.4 nM
	Baricitinib	110 nM	210 nM	**15 nM**	15 nM

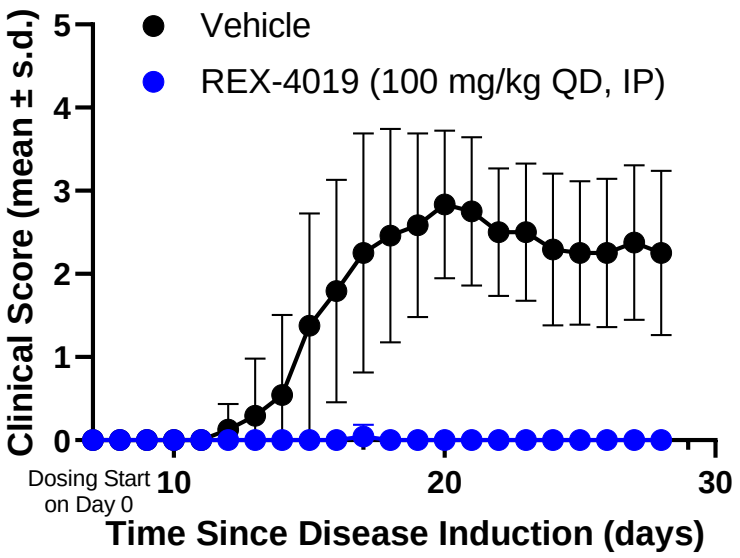
Selectivity relative to Th17 inhibition: >30X 10-30X <10X

STAT3 inhibition potently and selectively impairs the Th17 phenotype

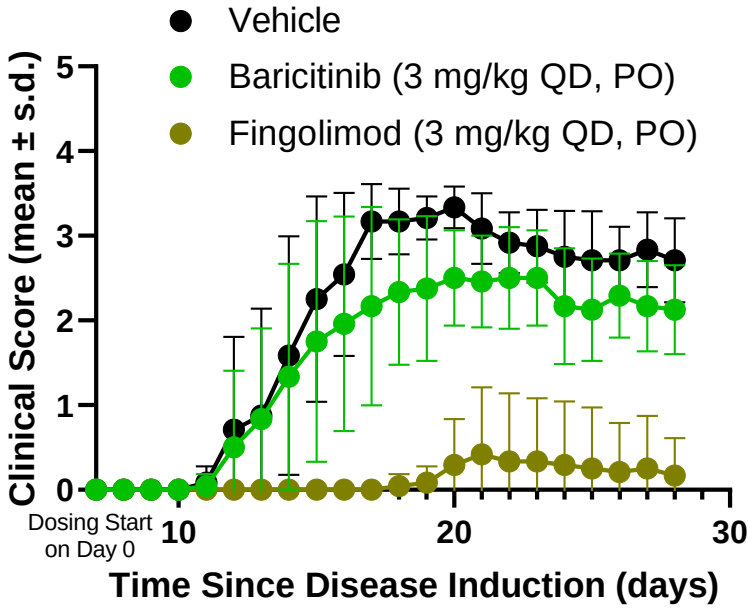
REX-4019 is active in mouse encephalomyelitis (EAE) model

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

Recludix Compound



Benchmark Compounds



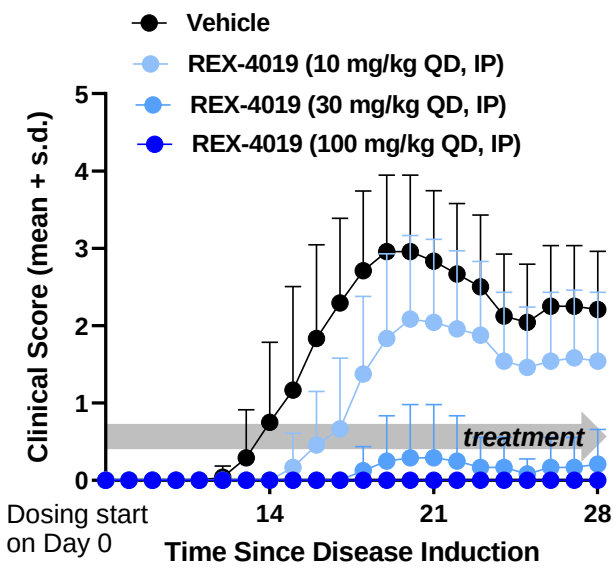
Proof-of-Concept that reversible small molecule STAT3 inhibition modulates in vivo Th17 disease

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

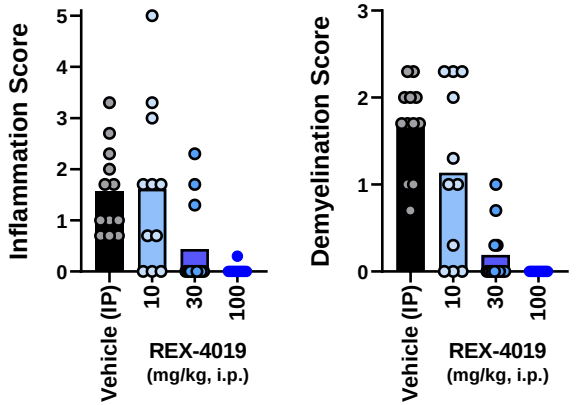
Prophylactic and therapeutic dose-dependent efficacy in the Th17-dependent EAE Model

Prophylactic

Neurological symptoms

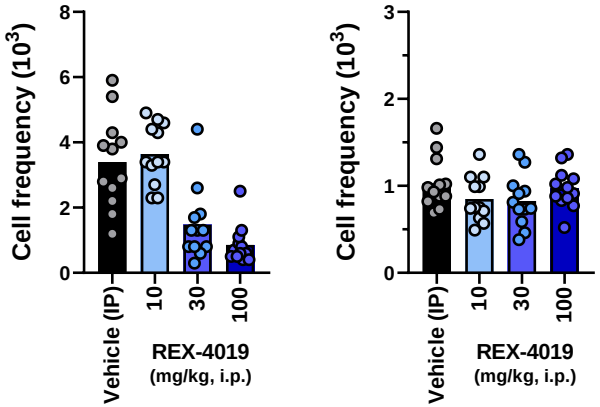


CNS tissue pathology

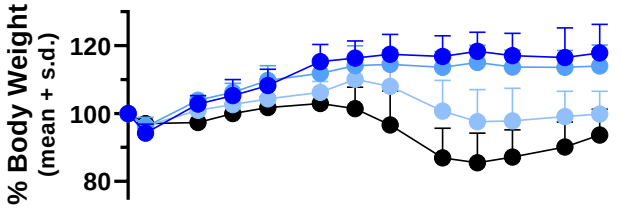


CNS Infiltrating Th17 cells

Peripheral Treg cells

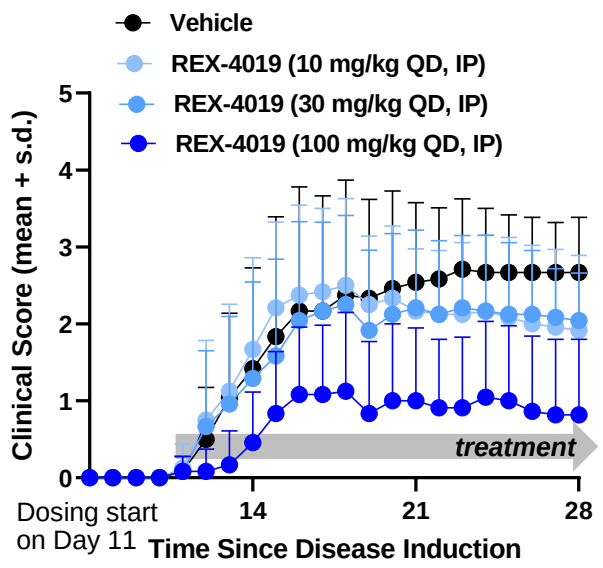


Inflammation-induced cachexia

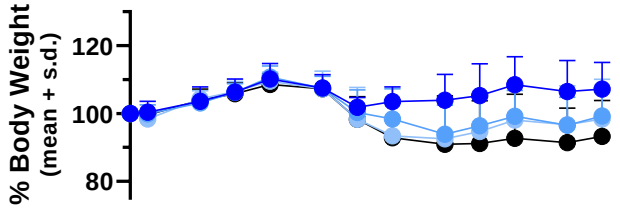


Semi-Therapeutic

Neurological symptoms



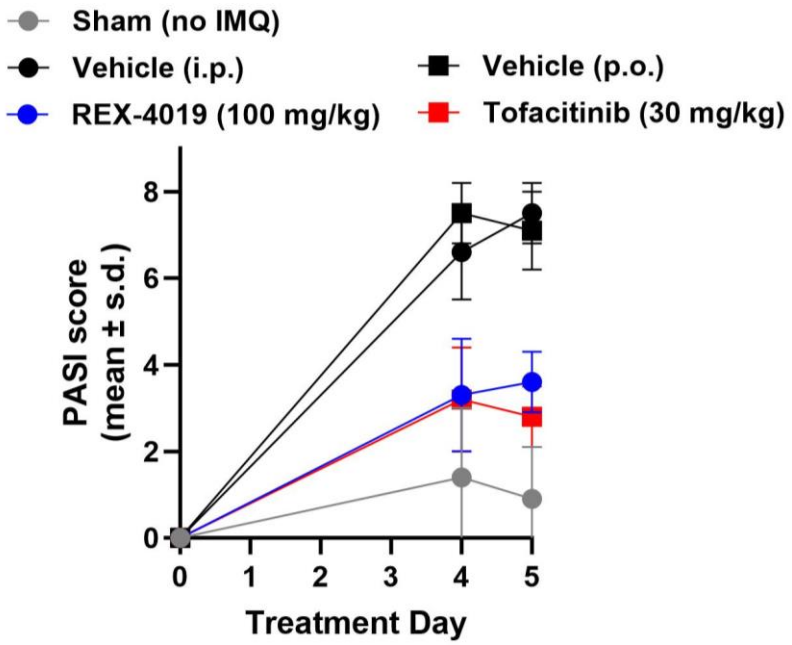
Inflammation-induced cachexia



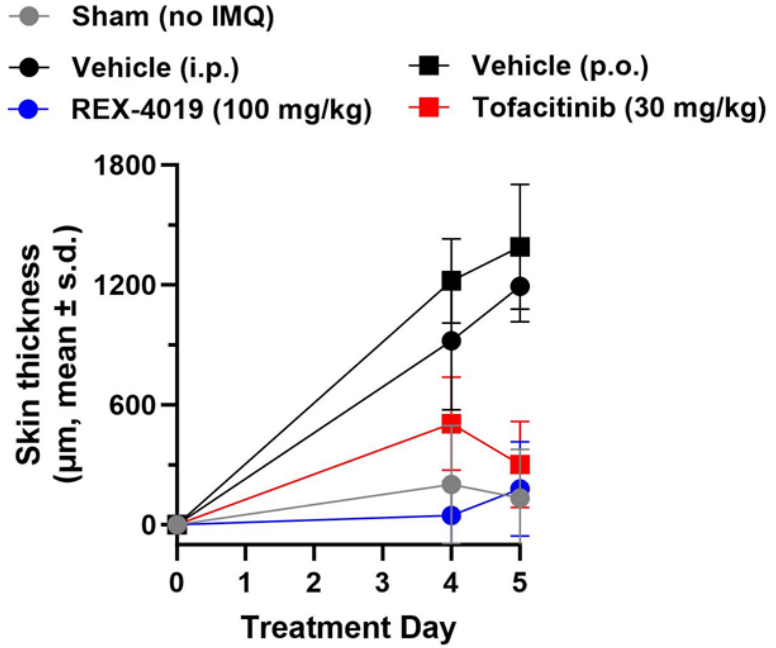
Selective STAT3 inhibition is efficacious in a Th17 dependent psoriasis model

- Imiquimod-induced psoriasis is responsive to anti-IL-17 and JAK/TYK2 inhibitor treatment

Clinical Score



Tissue Inflammation

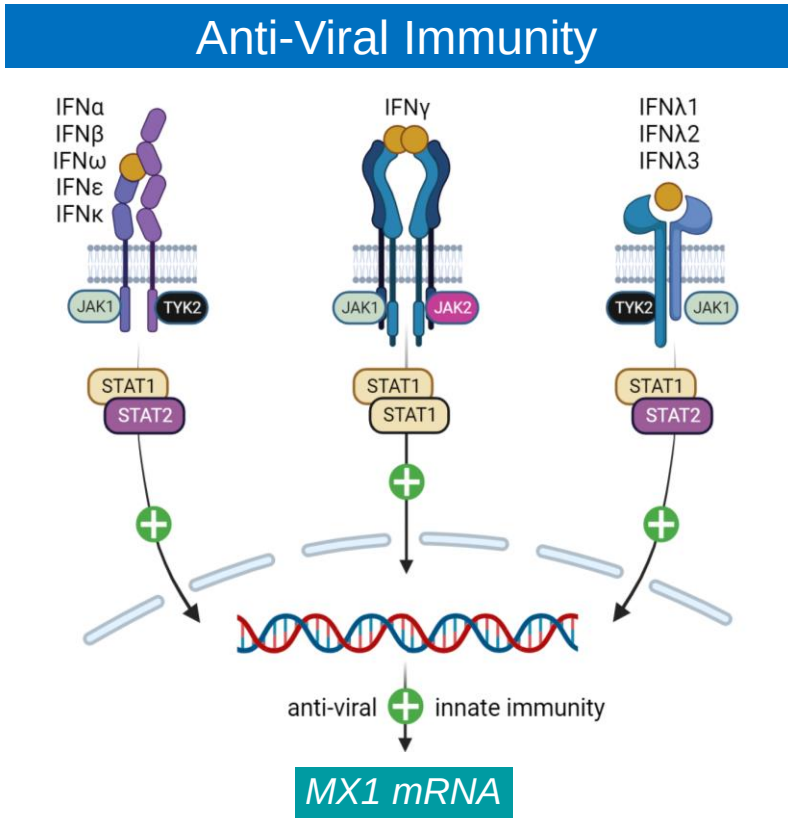


Proof-of-Concept that reversible small molecule STAT3 inhibition modulates Th17 mediated skin disease

van der Fits et al., J Immunol. 2009 May 1;182(9):5836-45
Works et al., J Immunol. 2014 Oct 1;193(7):3278-87.

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



		STAT3-driven Inflammation	STAT1/2-driven Anti-Viral Response	
		IL-6 STAT3 in PBMCs	IFNβ Response in Monocytes (MX1)	IFNγ Response in Monocytes (MX1)
STAT3 Inhibitors	**REX-4019**	**6.1 nM**	**960 nM**	**330 nM**
TYK2 Inhibitors	Deucravacitinib	**140 nM**	38 nM	570 nM
JAK Inhibitors	Tofacitinib	**110 nM**	1,400 nM	55 nM
	Upadacitinib	**48 nM**	130 nM	6.7 nM
	Baricitinib	**28 nM**	280 nM	9.7 nM

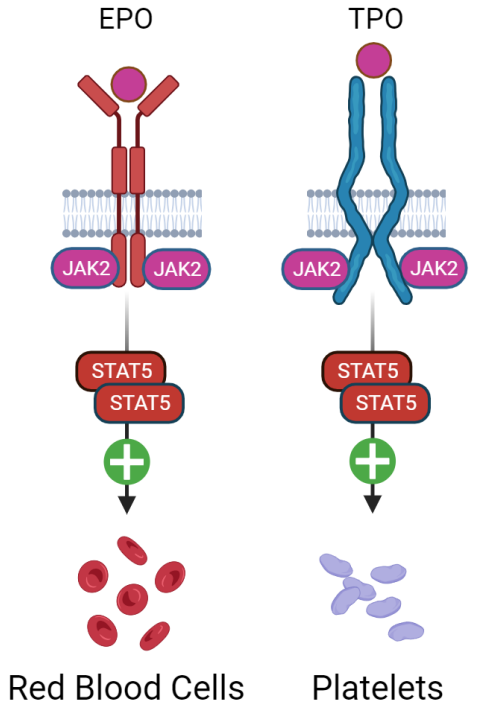
Selectivity relative to PBMC pSTAT3 inhibition: >30X 10-30X <10X

Targeting STAT3 may spare 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 reported cell lines

Hematology Homeostasis

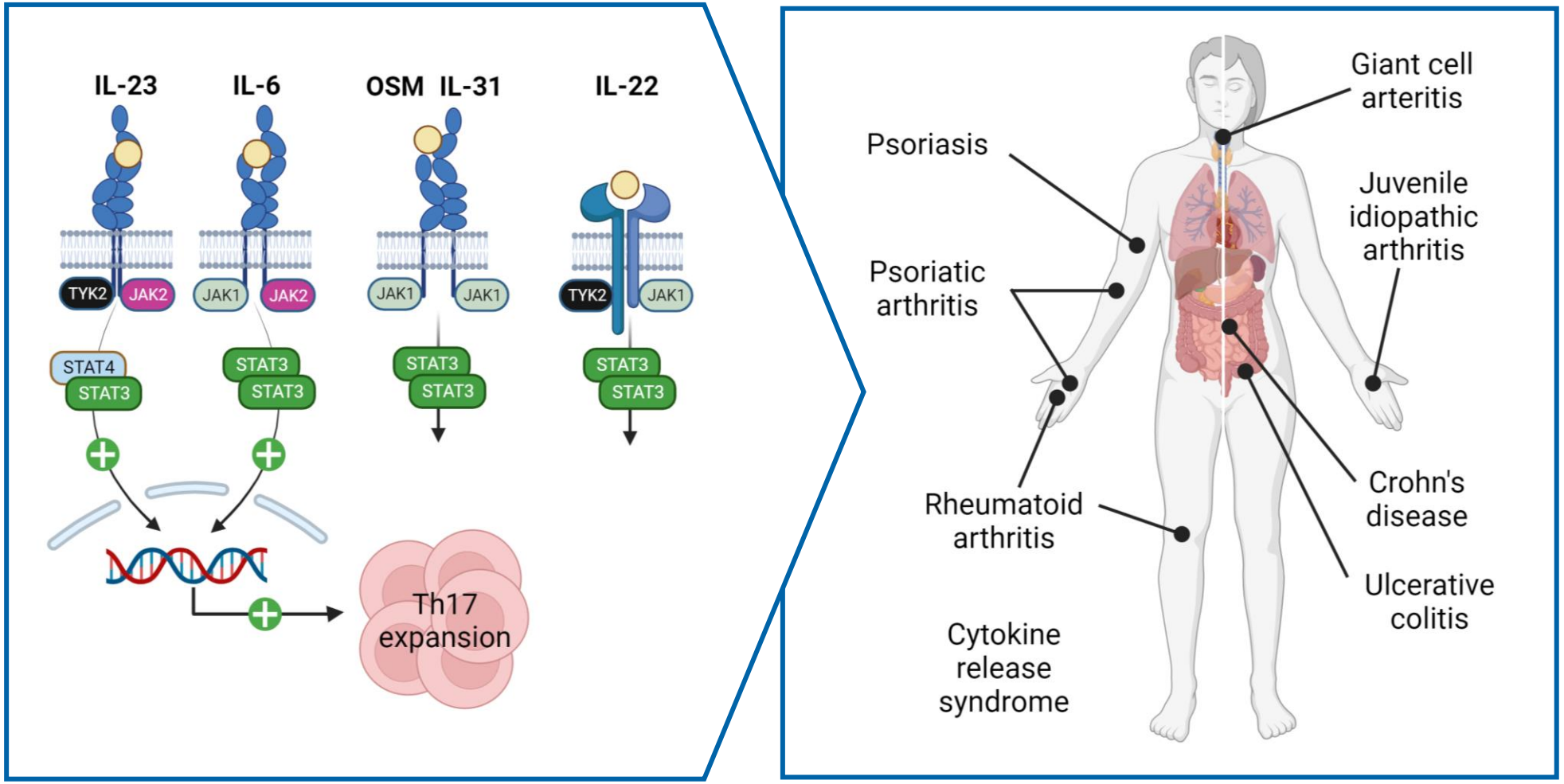


		STAT3-driven Inflammation	Erythropoiesis	Thrombopoiesis
		IL-6 STAT3 in PBMCs	EPO-Induced STAT5-Driven Transcription	TPO-Induced STAT5-Driven Transcription
STAT3 Inhibitors	**REX-4019**	**6.1 nM**	**>10,000 nM**	**>10,000 nM**
TYK2 Inhibitors	Deucravacitinib	**140 nM**	3,200 nM	250 nM
JAK Inhibitors	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 may 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

Drugging the ‘undruggable’ STAT3 target

- 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