Recludix Pharma

JP Morgan Healthcare Conference

January 2023

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

Unlocking New Therapeutic Possibilities

Unlocking Undruggable Targets in Cancer and Inflammatory Diseases

Recludix Pharma

Team with Exceptional Track Record

of solving complex, previously unsolvable problems resulting in multiple approved drugs

Experienced team drives success

Platform Company

that integrates custom designed DEL libraries, massively parallel SAR, and proprietary screening tools

Fuels the pipeline

Precision Oncology

and opportunities for broader oncology use, including immunooncology

Fastest path to POC

Inflammation & Autoimmunity

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

Significant market opportunity

Recludix Has Achieved In-Vivo POC in Multiple Animal Models Demonstrating Efficacy and Safety With Highly Selective STAT Inhibitors

Experienced Leadership and Top Tier Investors

Recludix Pharma

Nancy Whiting, Pharm.D. — CEO

Seagen, GSK

Adcetris®, Tukysa®, Padcev®, Tivdak®

Patrick Zarrinkar, Ph.D. — CSO

Wellspring, Pfizer, Blueprint, Ambit, GNF, MIT

Catherine Bovenizer, C.P.A. — SVP, Finance

Renova, Apricus, Ambit, Senomyx, Ligand, GeneFormatics

Matt Caldemeyer, MBA — CBO

Everest Medicines, Ambrx, Array, Amgen, Lilly

Brian Hodous, Ph.D. — SVP, Chemistry

Accent, Blueprint, Merck-Serono, Amgen, MIT

Ayvakit™

Daniel Treiber, Ph.D. — SVP, Discovery Technology

Eurofins, Discoverx, Ambit, MIT

Paul Smith, Ph.D. — SVP, Biology

Connect Biopharm, Incyte, Merck Serono, Novartis

Opelurza™

Nick Lydon, Ph.D. — Co-Founder, Board Member

Blueprint, AnaptysBio, Ambit, Amgen, Kinetix, Novartis/CIBA-GEIGY

Gleevec® (imatinib), Lasker-DeBakey Award, Japan Prize

$102M Series A

NEA

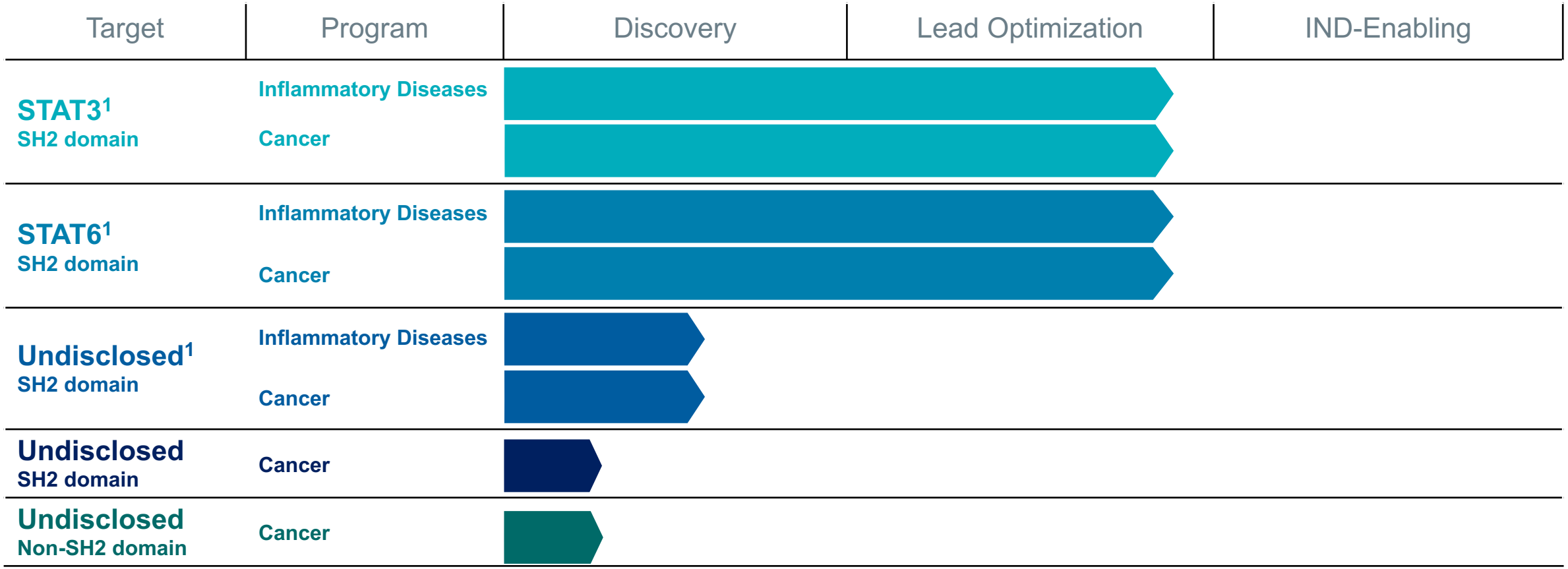
Access Industries

Westlake Village BioPartners

Nick Lydon

Broad Oncology and Immunology Pipeline

5 Targets, 8 Programs



[1]Separate molecules planned for cancer and inflammatory disease

Strong Progress in Advancing STAT3 and STAT6 Inhibitors Towards the Clinic

Recludix Pharma

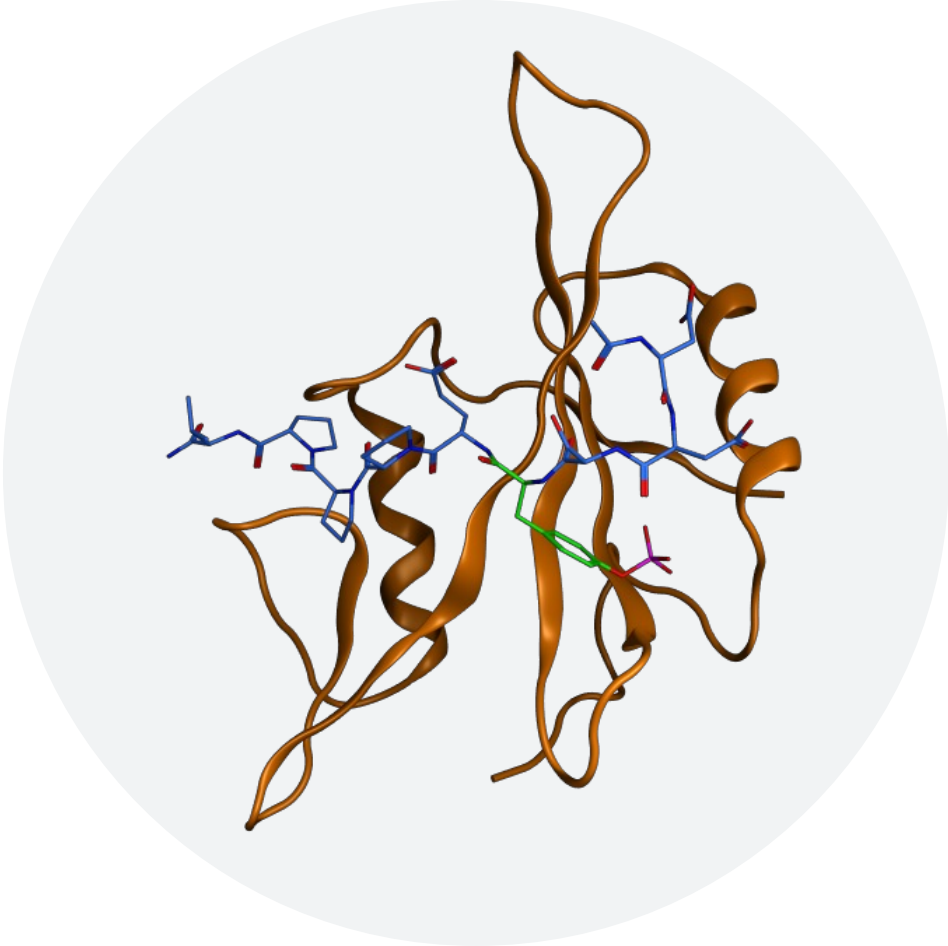
Accomplished To Date

- Built a novel, chemistry-focused platform to drug undruggable SH2 domains
- Discovered and generated potent, selective, reversible and orally bioavailable STAT SH2 domain inhibitors
- Demonstrated potent and selective activity in cell-based tumor and inflammatory disease models
- Demonstrated favorable differentiation from JAK and TYK2 inhibitors
- Demonstrated deep and durable target modulation in dogs
- Demonstrated in vivo efficacy in inflammation disease models

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



Recludix Platform: Integrated Proprietary Technologies & New Chemical Approaches

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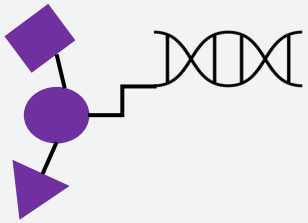
Discovery and SAR DELs

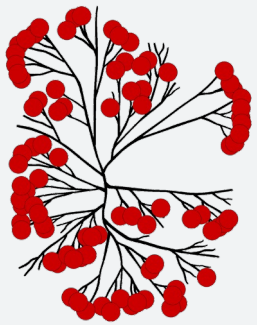
Millions of molecules



Custom DNA Encoded Libraries

Unique assay panel of SH2 domains

Drives selectivity

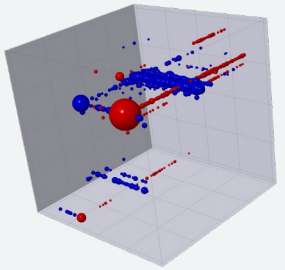


SH2 Domain Screening Tool

High Quality Lead Compounds

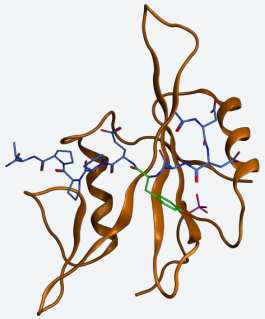
Proprietary DEL Selection & SAR Analysis

Rapid, massively parallel determination of structure-activity relationships



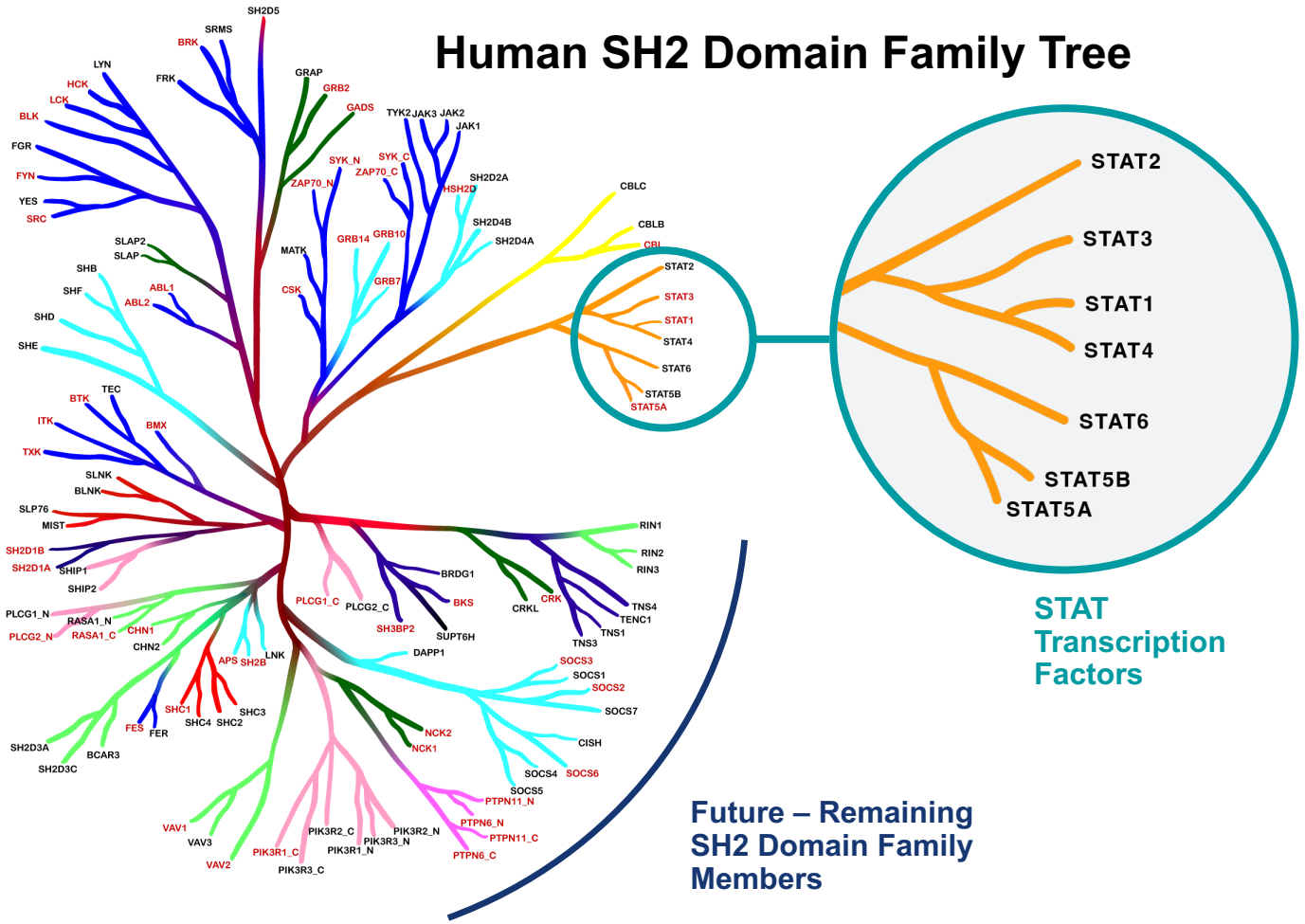
Structure-Based Design

Proprietary co-crystallography systems



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

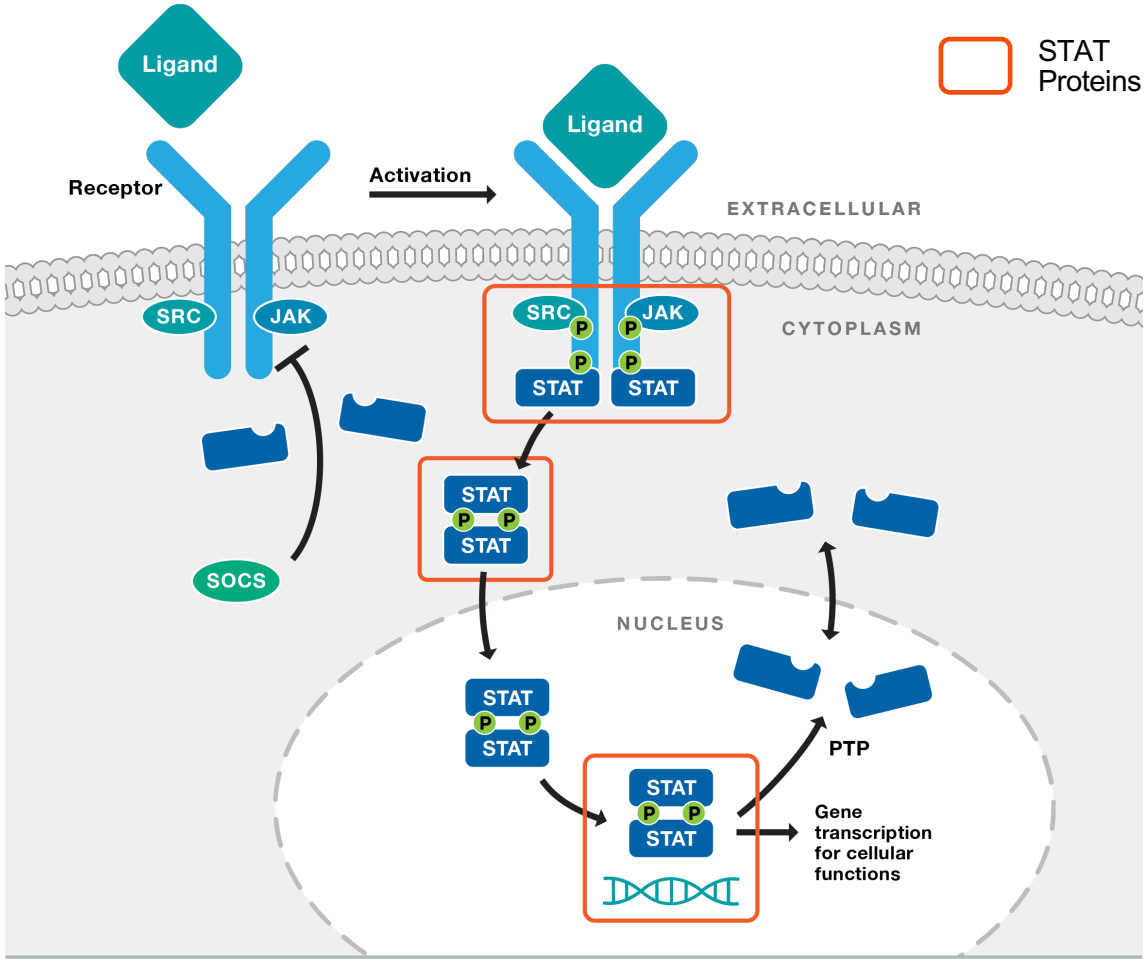
Molecular Cell (2006) vol. 22, p.851

STAT Transcription Factors Drive Oncogenic and Immune System 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 cancer and inflammatory diseases:

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



Nat. Rev. Drug Disc. (2013) vol.12, p.611

Selective STAT Inhibition Specifically Inhibits Disease Pathways

Recludix Pharma

Targeting STAT Proteins Provides a More Focused Impact on the Immune System than Targeting JAK/TYK2

	Efficacy Mechanisms				Anti-Viral Immunity		Hematologic Homeostasis	
	IL-6	IL-23	IL-4	IL-13	IFNα/β	IFNγ	EPO	TPO
STAT6 Inhibitor			+	+				
Dupixent®			+	+				
STAT3 Inhibitor	+	+						
Actemra®	+							
Skyrizi®		+						
JAK inhibitors	+	+	+	+	+	+	+	+
TYK2 inhibitors		+			+			

- Oral, specific STAT3 and STAT6 inhibitors have therapeutic potential across a range of inflammatory disease indications, including rheumatology and dermatology, while reducing impact on mechanisms associated with safety concerns
- JAK and TYK2 inhibitors impact mechanisms important for viral immunity and hematologic homeostasis

Recludix's Reversible, Oral, Small Molecule STAT Inhibitors are Differentiated from Competitors

Recludix Pharma

	Recludix's STAT Inhibitors	JAK/TYK2 Inhibitors	Biologics	Degraders	Antisense Oligo-nucleotides
Potent	+++	+++	++++	+++	++
Selective	++++	+	++++	+++	++
Reversible	++++	++++	+	+	+
Oral	++++	++++	-	+/-	+/-
Resistance Mechanisms	++	++	+	++++	+

STAT6

STAT6 – An Opportunity to Disrupt a Global Multi-Billion Dollar Market With an "Oral Dupixent"

STAT6 Mutant or Activated Heme Malignancies

- Early POC opportunity, potential for responses in dose escalation
- STAT6 activated populations (US annual incidence) ~7K DLBCL, ~6K HL, ~5K FL

STAT6 Tumor Infiltrating Macrophages

- Single agent or combination with checkpoint inhibitors in solid tumors could represent a new paradigm in immuno-oncology

STAT6 mutant or activated across a range of lymphomas

STAT6 down-modulation converts immuno-suppressive M2 macrophages to M1 phenotype

IL-4/IL-13 signaling through STAT6 is critical in Th2 driven disease

Th2-mediated Inflammatory Diseases

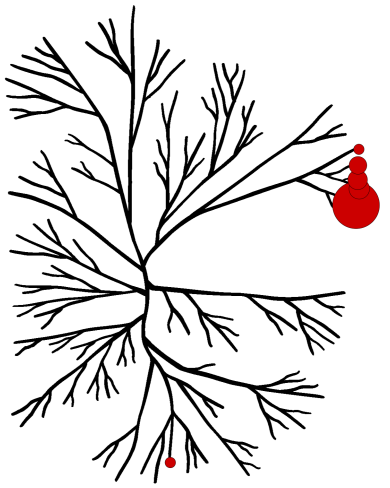
- Potential for superior profile with oral modality with leading treatments
  - DUPIXENT®, an injectable IL-4Ra inhibitor, annual sales >$4B in 2021, with forecast peak sales of >$14B
- Small molecule format may also enable topical or inhaled formulation, potentially supporting use before injectable biologics

STAT6 Early Lead Compound REX-2787 is Potent and Selective in Biochemical and Cellular Assays

Recludix Pharma

Current Lead Compounds Further Optimized

REX-2787

Biochemical Potency (SH2scan K_D)	Cellular Potency (pSTAT6 IC_{50} in human PBMCs)	Biochemical STAT Family Selectivity	Cellular Selectivity (PBMCs)	SH2 Domain Selectivity
0.73 nM	16 nM	>250X vs. STAT1/2/3/4/5	~70X to >1,000X vs. STAT1/2/3/4/5	

Selective STAT6 Inhibitor Phenocopies Dupilumab In T Cell Functional Assays

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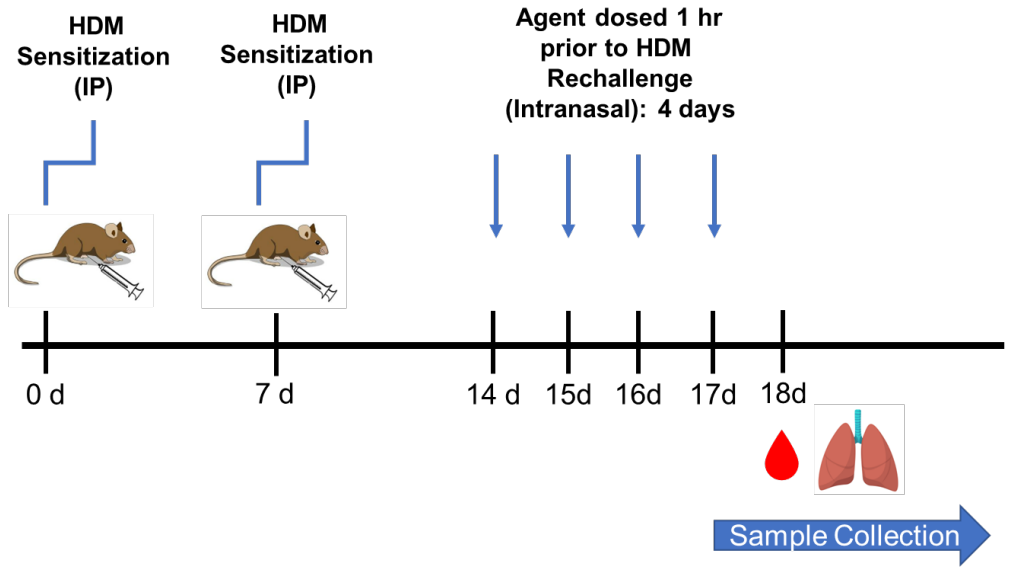
Selective STAT6 Inhibitor Does Not Impact STAT6-independent T Cell Functions, Unlike Broadly active JAK Inhibitors

		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, IL-13)**
STAT6 Inhibitor	**REX-2787**	>10,000 nM	>6,000 nM	>10,000 nM	**240 nM**
IL-4/IL-13 Antagonist	Dupilumab	>10,000 nM	>1,000 nM	>1,000 nM	**26 nM**
JAK Inhibitors	Abrocitinib	1,300 nM	900 nM	73 nM	**80 nM**
	Upadacitinib	39 nM	36 nM	7.4 nM	**4.3 nM**
	Baricitinib	100 nM	210 nM	25 nM	**15 nM**

> 10X selectivity relative to Th2 inhibition

< 10X selectivity relative to Th2 inhibition

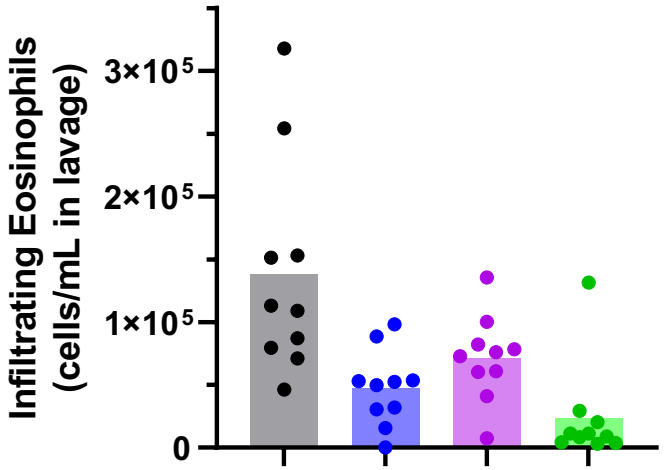
Recludix STAT6 Inhibitors Reduce Lung Inflammation in House Dust Mite (HDM) Allergy Model



- First demonstration of efficacy in a disease model for any STAT6 inhibitor
- Proof-of-Concept that reversible small molecule STAT6 inhibition modulates disease

Eosinophils Present in Bronchoalveolar Lavage

- Vehicle (IP)
- REX-3922 (100 mg/kg QD, IP)
- REX-3956 (100 mg/kg QD, IP)
- Dexamethasone (1 mg/kg QD, PO)



REX-2787 Inhibits STAT6-Mediated Cell Growth in a STAT6-Mutant Lymphoma Cell Line

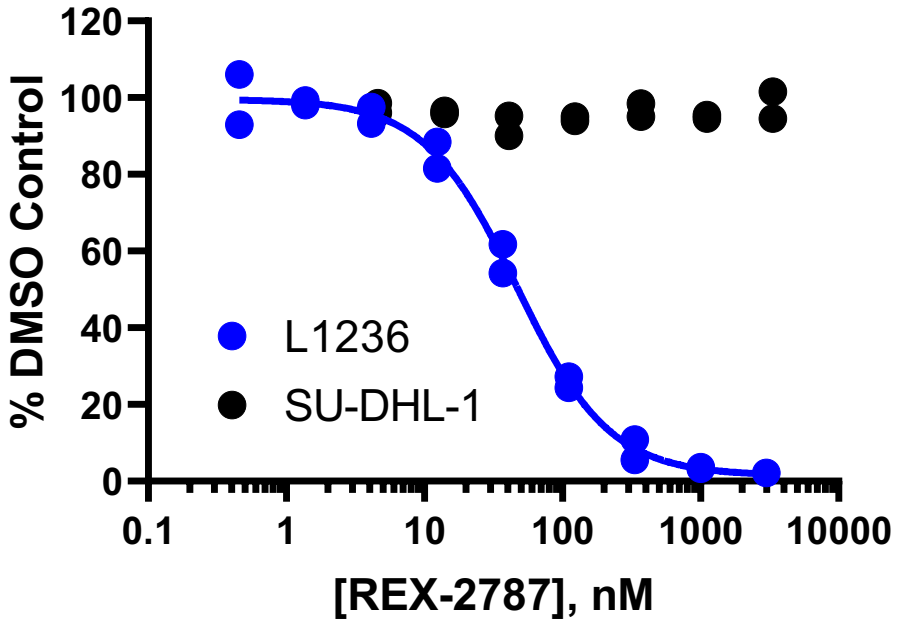
L1236 Cell Line (Hodgkin Lymphoma)

- STAT6(D419N/N417Y) mutant
- IL-13 expressing
- STAT6-dependent (DepMap)

REX-2787

Cell Growth IC_{50}	**L1236**	47 nM
	SU-DHL-1 (STAT6-independent Control)	>3,000 nM
pSTAT6 IC_{50} (3 hr)		18 nM

Cell Growth – 3 days



STAT3

STAT3 – First and Best-In-Class Opportunity to Drug a Previously Undruggable 'Holy Grail' Target

Recludix Pharma

STAT3 Mutant or Activated Heme Malignancies

- Early POC opportunity, potential for responses in dose escalation
- STAT3 activated populations (U.S. annual incidence): ~7K DLBCL, ~8K AML, ~2.8K CTCL, ~2K ALCL, ~2K MPN

STAT3 Activated Solid Tumors

- STAT3 is a "holy grail" target with significant opportunity in STAT3 activated cancers

STAT3 Immunosuppressive TME

- Combination with checkpoint inhibitors could represent a new paradigm in immuno-oncology

> 70% of human cancers exhibit abnormally elevated STAT3 activation

STAT3 is a driver of Th17 inflammatory cells

TH17 Inflammatory Diseases where JAK inhibitors have proven effective

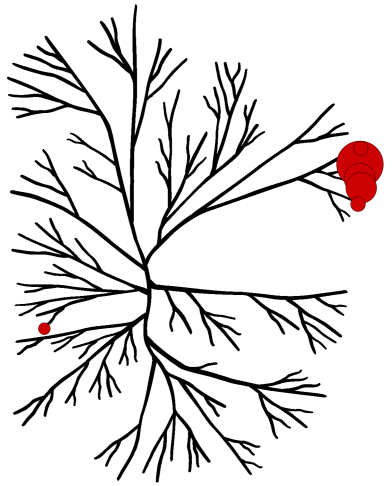
- Increased selectivity provides both greater efficacy and less toxicity than JAK inhibitors
- While TYK2 inhibitors have improved selectivity over pan-JAKs, biological selectivity of targeting STAT3 is greater
- For example, SKYRIZI®, an injectable IL-23 inhibitor, annual sales $3B in 2021
- JAK inhibitor global sales >$4.7B annually, despite Black Box safety warnings

STAT3 Early Lead Compound REX-2317 is Potent and Selective in Biochemical and Cellular Assays

Recludix Pharma

Current Lead Compounds Further Optimized

REX-2317

Biochemical Potency (SH2scan K_D)	Cellular Potency (pSTAT3 IC_{50} in human PBMCs)	Biochemical STAT Family Selectivity	Cellular Selectivity (PBMCs)	SH2 Domain Selectivity
0.83 nM	5.2 nM	>20X vs. STAT1/4 >1,000X vs. STAT2/5/6	12X vs. STAT1 40X to >2,000X vs. STAT4/5/6	

Selective STAT3 Inhibitors are Differentiated From JAK and TYK2 Inhibitors in T Cell Functional Assays

Recludix Pharma

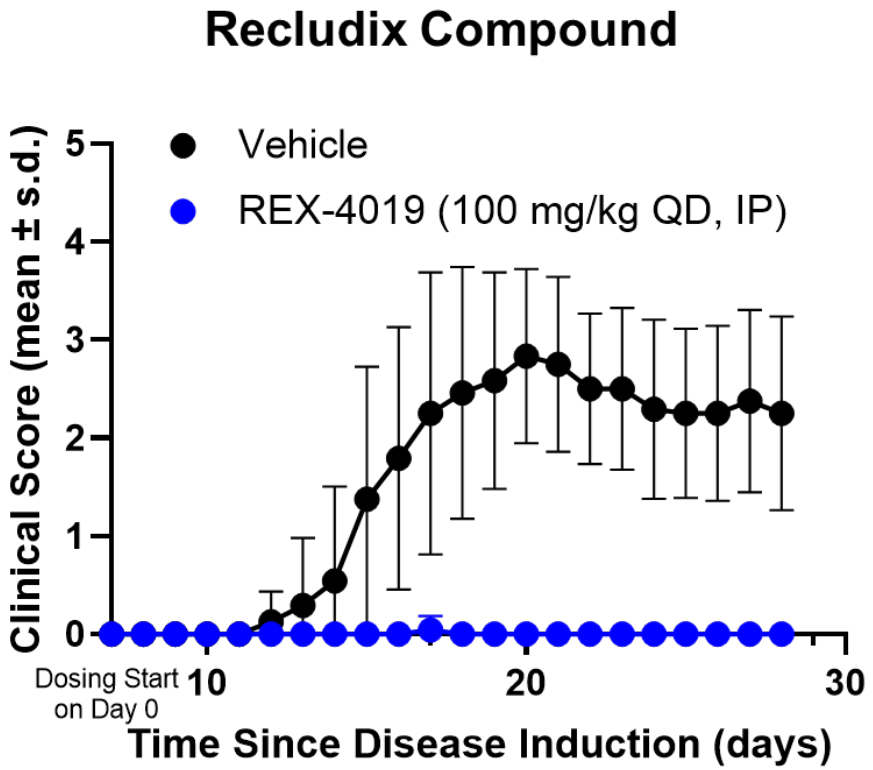
Direct Selective STAT3 Inhibition Provides Greater Selectivity Than JAK or TYK2 Inhibitors

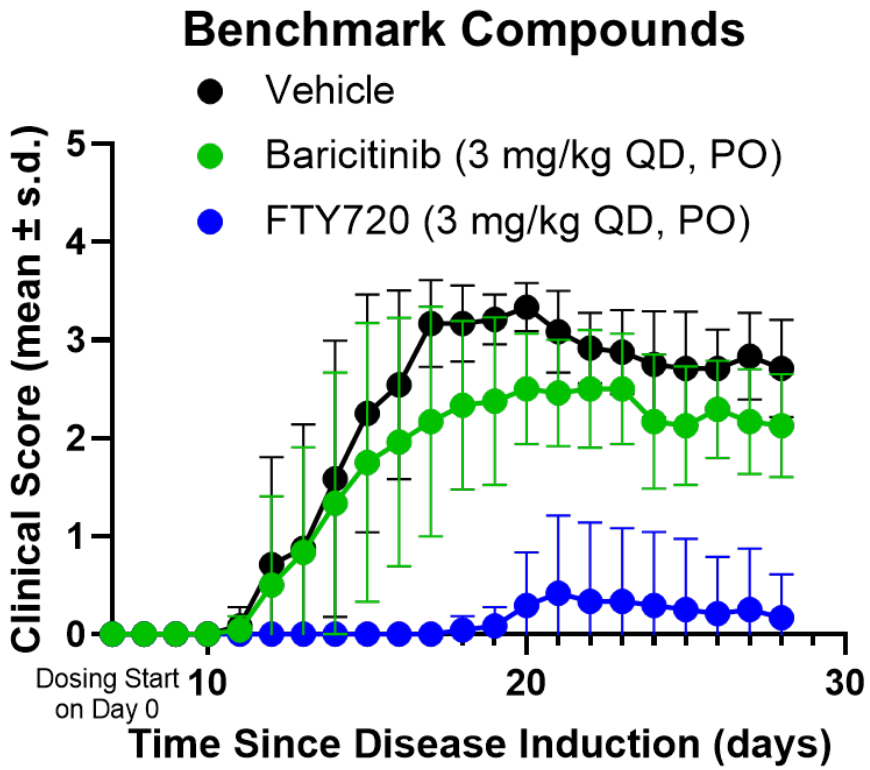
		General Adaptive Immune Response	Defense Against Viruses and Bacteria	Defense Against Extracellular Pathogens	Defense Against Parasites and Mediation of Antibody Responses
		T Cell Activation (CD25)	**Th1 Cell Function (IFNγ)**	**Th17 Cell Function (IL-17A)**	**Th2 Cell Function (IL-5)**
STAT3 Inhibitor	**REX-2317**	>10,000 nM	>2,000 nM	**14 nM**	>10,000 nM
IL-6 Antagonist	Tocilizumab	>1,000 nM	>1,000 nM	**In progress**	>1,000 nM
IL-23 Antagonist	Risankizumab	>1,000 nM	>1,000 nM	**In progress**	>1,000 nM
TYK2 Inhibitor	Deucravacitinib	>3,000 nM	260 nM	**37 nM**	>1,000 nM
JAK Inhibitors	Tofacitinib	340 nM	74 nM	**36 nM**	20 nM
	Upadacitinib	39 nM	36 nM	**7.4 nM**	4.3 nM
	Baricitinib	100 nM	210 nM	**25 nM**	15 nM

> 10X selectivity relative to Th17 inhibition

< 10X selectivity relative to Th17 inhibition

REX-4019 Is Active In Mouse Autoimmune Encephalomyelitis (EAE) Model





- First demonstration of efficacy in a disease model for a Recludix STAT3 inhibitor
- Proof-of-Concept that reversible small molecule STAT3 inhibition modulates disease

REX-2317 Inhibits STAT3-Driven Transcription and Cell Growth in ALK+ ALCL Models

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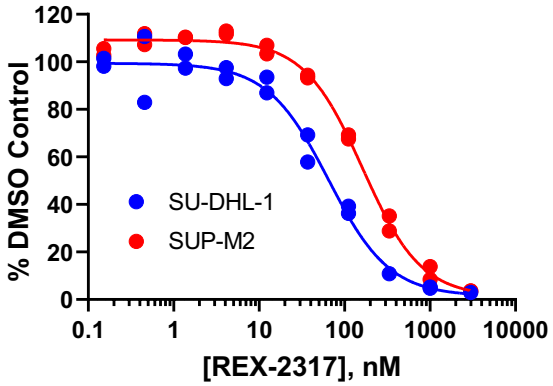
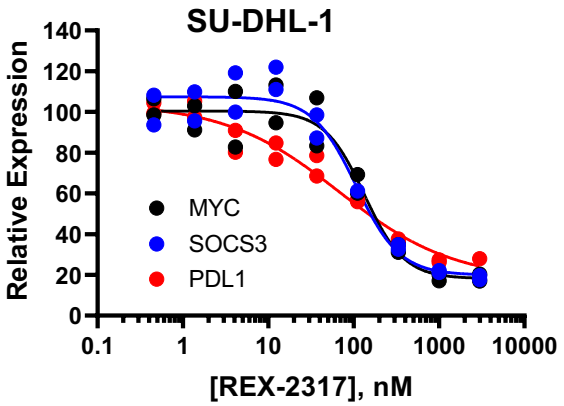
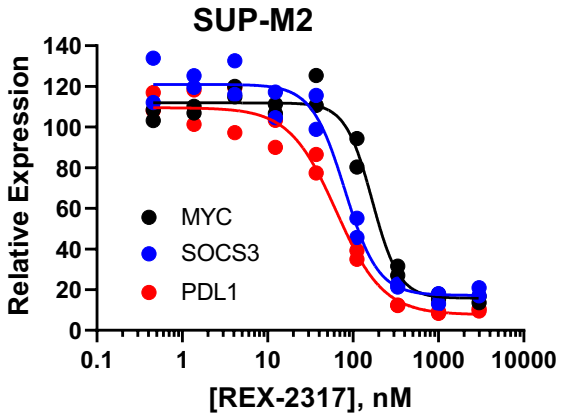
pSTAT3 Inhibition (3 hrs)

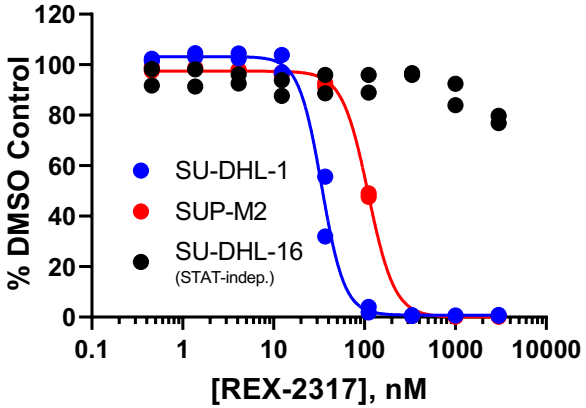


STAT3-Driven Transcription Inhibition (20 hrs)





Cell Growth Inhibition (4-5 days)



Assay	IC_{50}
pSTAT3	
SU-DHL-1	65 nM
SUP-M2	160 nM
STAT3-driven transcription	60-180 nM
Cell Growth	
SU-DHL-1	34 nM
SUP-M2	110 nM

Strong Progress in Advancing STAT3 and STAT6 Inhibitors Towards the Clinic

Near Term Milestones

- Complete lead optimization
- Demonstrate in vivo efficacy in additional models of cancer and inflammatory disease
- Initiate preliminary toxicology studies
- Development candidate nomination in 2023
- Initiate Phase 1 clinical trials in 2024

Recludix is Well Positioned to be the Leader in SH2-Targeted Therapeutics

Recludix Pharma

Foundational Platform with Experienced Team

- Custom DNA-Encoded Libraries
- Proprietary DEL Selection and SAR Analyses
- Structure-Based Drug Design
- Family-Wide Screening Tools

First Applications in SH2 Domain Inhibitors

Five high-interest targets in cancer & inflammatory diseases › Early POC opportunity in precision oncology › Increased selectivity and oral administration are differentiating and expand therapeutic window

Pipeline Opportunities Beyond SH2 Domain

Recludix Pharma

Thank you

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Unlocking New Therapeutic Possibilities