Recludix platform has unlocked development of oral, reversible small molecule inhibitors of SH2 domains

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Introduction

Many critical intracellular proteins ranging from kinases to adapter molecules to transcription factors mediate signaling via interaction of their SH2 domain with phosphorylated tyrosine residues. Until now, it has not been feasible to develop oral small molecule SH2 inhibitors that directly target this interaction. Recludix has built a platform that has allowed discovery of such inhibitors via custom-designed DNA-encoded libraries and proprietary tools to determine structure-function relationships. Numerous crystal structures of SH2 domains bound to inhibitors have been generated providing critical insights into SH2 inhibition. Lastly, a validated prodrug platform has been adapted to generate molecules with good oral bioavailability. The first three targets in the Recludix pipeline are the STAT6 and STAT3 transcription factors and BTK. Data will be presented on all three programs showing discovery of molecules with high biochemical and cellular potency. Additional data will show evidence of high target engagement and efficacy across a range of cellular assays and preclinical models of autoimmune disease. The lead molecule from the STAT6 program is progressing towards clinical development in 2026. Inhibitors of the BTK SH2 domain show potential for differentiation from kinase inhibitors with the first development candidate expected in 2026. SH2 domains have previously been considered undruggable but the Recludix platform has opened the door to some of the most compelling targets in Immunology and across therapeutic areas.

Methods

The Recludix Pharma SH2 domain discovery platform integrates custom and proprietary DNA-encoded libraries (DEL), structure-based design enabled by rapid STAT SH2 domain crystallography, and a biochemical assay panel to assess selectivity and potency across the SH2 domain family **(Figure 1)**.

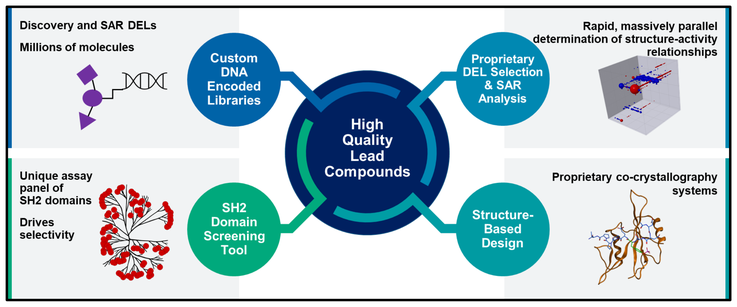


Figure 1. Integrated SH2 domain drug discovery and chemical optimization platform

Proprietary DEL libraries identify novel hits which feed into crystallography for rapid structure-based drug design optimization. Optimization of leads uses structure-based drug design, *in silico* optimization, focused DEL libraries and a suite of biochemical and biophysical assays to monitor potency and physicochemical properties. STAT3 exemplifies the value of this integrated approach to target previously undruggable targets.

Structural Enablement

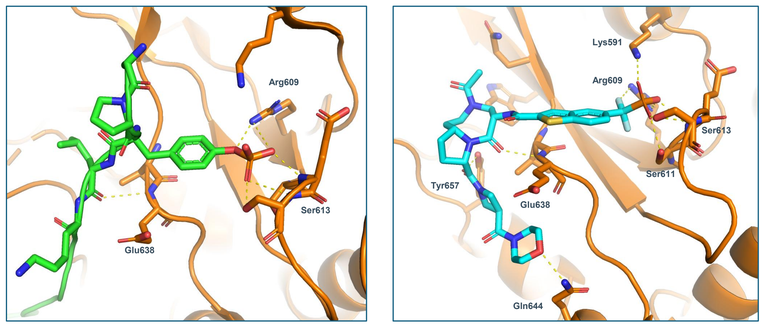
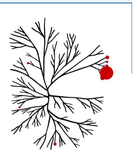


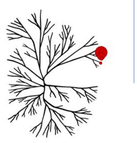
Figure 2. Recludix's chemical matter occupies the phospho-tyrosine binding pocket of the SH2 domain

Left: STAT3 tyrosine phosphorylation (pY705; green) induces homodimerization of the STAT3 protein (orange), triggering nuclear localization and pro-inflammatory transcriptional activity (PDB: 6QHD)

Right: Competitive inhibition with an optimized peptidomimetic compound (cyan) prevents dimerization in vitro and in vivo and renders STAT3 inactive. Structurally-enabled optimization of phosphotyrosine mimetic inhibitors maximize hydrogen bonding and VDW contacts to improve binding affinity over the natural pY705 substrate.

Novel, Potent, and Selective Inhibitors of STAT Transcription Factors

	Biochemical potency (SH2scan K_D)	Cellular potency (pSTAT6 IC_{50} in human PBMCs)	Biochemical STAT family selectivity	Cellular selectivity (PBMCs)	SH2 domain selectivity
REX-8756 STAT6i	0.04 nM	0.72 nM (IL-4) 0.19 nM (IL-13)	>1,000X vs. STAT1/2/3/4/5	>1,000X vs. STAT1/2/3/4/5	

	Biochemical potency (SH2scan K_D)	Cellular potency (pSTAT3 IC_{50} in human PBMCs)	Biochemical STAT family selectivity	Cellular selectivity (PBMCs)	SH2 domain selectivity
REX-7117 STAT3i	0.16 nM	1.2 nM (IL-6)	~20X vs. STAT1 >500X vs. STAT2/4/5/6	~20X vs. STAT1 >500X vs. STAT2/4/5/6	

Results – STAT6

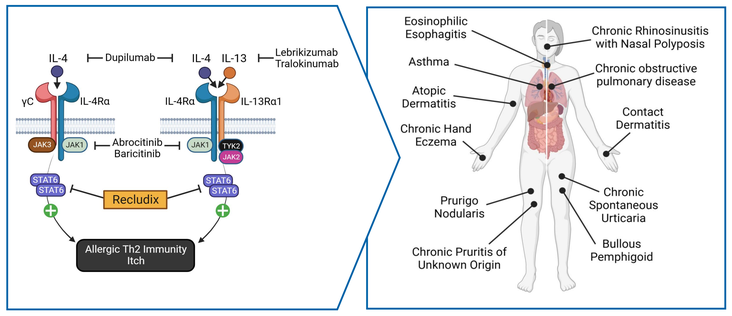
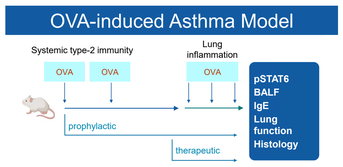


Figure 3. IL-4/IL-13 activity is dependent on downstream STAT6 intracellular signaling. Clinical trials targeting the IL-4/IL-13 pathway have reported significant efficacy in multiple human autoimmune and inflammatory diseases.

REX-4671, a rodent tool molecule, demonstrates comparable efficacy to combined anti-IL-4/13 rodent surrogate antibodies when dosed prophylactically in a mouse ovalbumin (OVA) asthma model.



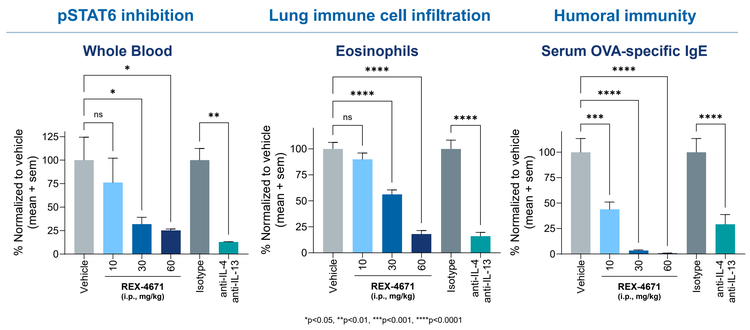


Figure 4. STAT6i reduces lung inflammation in a mouse ovalbumin (OVA) asthma model.

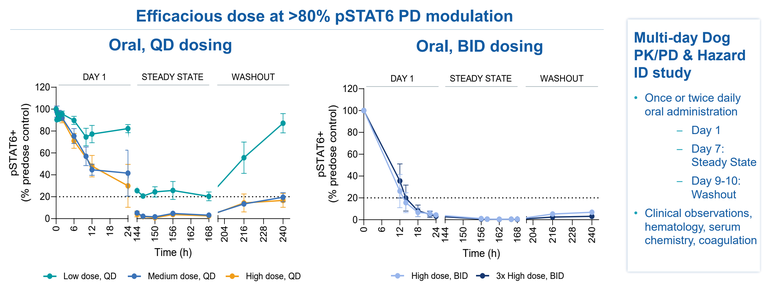


Figure 5. REX-8756 achieves complete pSTAT6 inhibition with once daily dosing and is well tolerated in dog 7-day PK/PD and hazard ID study. REX-8756 is highly selective for pSTAT6 inhibition in vivo, no off-target pSTAT1 or pSTAT3 inhibition was observed in dog PBMC's. REX-8756 was well tolerated at all dose levels.

STAT3

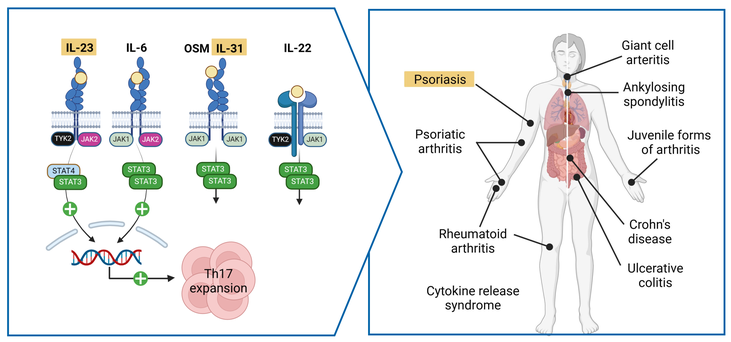


Figure 6. Multiple proinflammatory and pruritic cytokines are dependent on downstream STAT3 intracellular signaling. Clinical trials selectively targeting many of these cytokines has validated their contribution to human autoimmune and inflammatory diseases

The murine IL-23 induced psoriasis model is well established for the evaluation of novel therapeutics targeting the Th17 pathway. In head-to-head studies, REX-7117 achieved efficacy responses similar to an anti-IL-17A surrogate treatment and was more efficacious than deucravacitinib at an estimated clinically relevant dose (**Figure 7**).

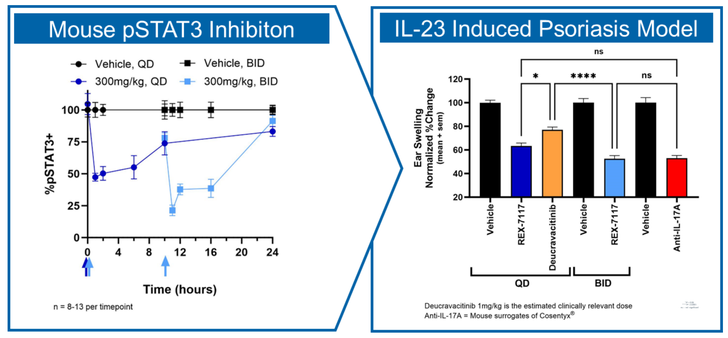


Figure 7. Oral dosing of REX-7117 in mice mimics the dog pSTAT3 pharmacodynamic response (data shared previously). REX-7117 demonstrates efficacy comparable to an anti-IL-17 benchmark in a murine cytokine-induced psoriasis model.

BTK

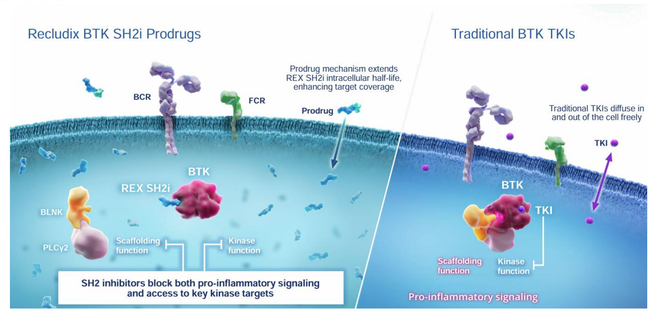


Figure 8. Inhibition of the SH2 domain disrupts both the kinase and scaffolding functions of BTK. Our Recludix prodrug technology generates high intracellular concentrations of active drug to improve target coverage

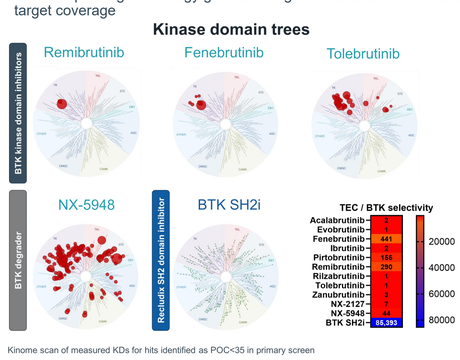


Figure 9. All current BTK TKIs and degraders have affinity for the off-target TEC associated with platelet dysfunction. Recludix BTK SH2 inhibitors are highly potent in functional cellular assays (< 5 nM for BCR-mediated ERK activation and CD69 expression in B cells) and represent the most selective BTK inhibitors identified to date (>69,000-fold vs TEC and >8,000-fold vs the SH2ome in SH2scan).

Kinome scan of measured KDs for hits identified as POC<35 in primary screen

Recludix BTK SH2i achieve deep and durable target engagement that leads to dose-dependent reduction in skin inflammation in a mouse preclinical CSU model following single-dose prophylactic treatment, similar to clinically-approved BTK TKIs **(Figure 10)**.

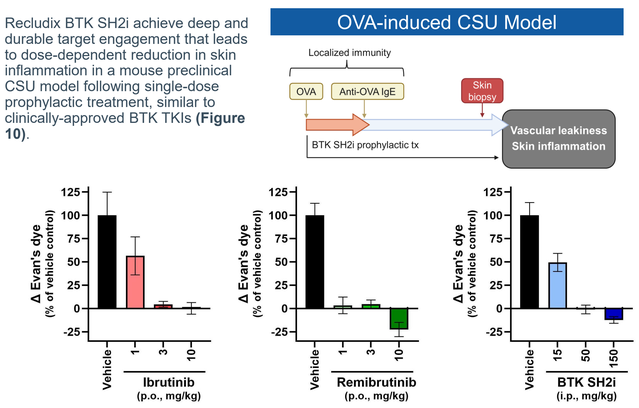


Figure 10. BTK SH2i reduce skin inflammation in a clinically-relevant model of CSU.

Conclusions

The Recludix Platform has achieved direct targeting of SH2 domain-containing proteins with compounds which have potential to be oral and reversible

The ability of the platform to directly target the SH2-phosphotyrosine interaction, while taking advantage of unique cryptic pockets in each domain, enable highly potent and selective inhibitors

The platform has enabled advanced programs targeting transcription factors (STAT3 and STAT6) and kinases (BTK)

The Sanofi-partnered STAT6 Program is anticipated to reach the clinic by early 2026

Recludix highly interested in academic partnerships to define the next wave of SH2 targets for targeting by our platform

Illustrations generated using Biorender.com software

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