Novel inhibitors of the BTK SH2 domain selectively and potently block BTK signaling and are efficacious in preclinical models of chronic spontaneous urticaria

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Background

BTK signaling in multiple immune cell types is important in immunological diseases such as chronic spontaneous urticaria (CSU), rheumatoid arthritis, and multiple sclerosis. BTK supports pro-inflammatory signaling downstream of the Fc receptor and B cell receptor through formation of signaling complexes dependent on the BTK SH2 domain. Achieving clinical efficacy with BTK tyrosine kinase inhibitors (TKIs) has been compromised by failure to maintain deep and durable inhibition of BTK's kinase activity. Additionally, off-target inhibition of TEC kinase has been implicated in adverse events related to platelet dysfunction, such as bleeding and petechiae. Inhibiting BTK with Recludix platform small molecule prodrugs has the potential to improve efficacy by maintaining high intracellular concentrations of active drug. Furthermore, targeting the BTK SH2 domain offers an opportunity to greatly enhance target selectivity.

Although no BTK inhibitors are yet approved for dermatologic diseases, remibrutinib (Novartis) has demonstrated Phase 3 efficacy in CSU and encouraging Phase 2 data in hidradenitis suppurativa.

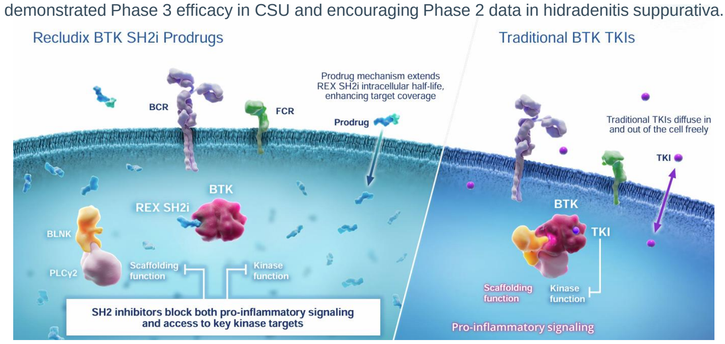


Figure 1. Inhibition of the SH2 domain disrupts both the kinase and scaffolding functions of BTK. Our Recludix prodrug technology generates high intracellular concentrations of active drug to improve target coverage

Methods & Technology

The Recludix Pharma SH2 domain discovery platform integrates custom and proprietary DNA-encoded libraries (DEL), structure-based design enabled by rapid BTK SH2 domain crystallography, and a biochemical assay panel to assess selectivity and potency **(Figure 2)**

Figure 2. Integrated SH2 domain drug discovery and chemical optimization platform.

Our prodrug approach facilitates optimization of durable cellular PK and target engagement. Discovery of potent and selective BTK inhibitors exemplifies the value of this integrated approach to target previously undruggable domains and targets

Data Results

Recludix has identified highly potent BTK SH2 domain inhibitors, exemplified here by BTK SH2i, that demonstrate best-in-class selectivity across a comprehensive panel covering ~75% of human SH2 domains; overall >8000 selectivity against SH2ome was observed **(Table 1)**

	BTK SH2i	
Biochemical Potency (BTK K_d)	0.055 nM	**SH2 Family Selectivity**
Biochemical Selectivity (TEC and SH2ome)	>69,000 × vs. TEC >8000× vs SH2ome	
Cellular Cytotoxicity (CTG IC_{50} in Jurkat cells)	>10,000 nM	

Table 1. Discovery of novel, potent, and selective BTK SH2 domain inhibitors

Broader off-target profiling across the kinome revealed that the Recludix SH2 inhibitors demonstrate exquisite selectivity

Unlike many BTK TKIs, the Recludix Pharma BTK SH2i did not inhibit TEC kinase, an important off-target involved in platelet dysfunction (Figure 3). Typically, SH2 domains are associated with greater structural diversity than the ATP binding domain

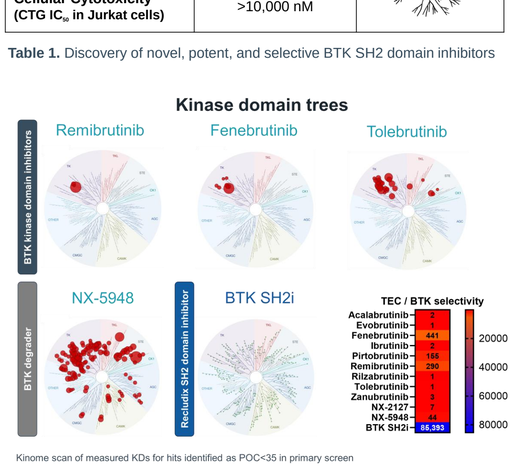


Figure 3. All current BTK TKIs and degraders have affinity for the off-target TEC associated with platelet dysfunction. Recludix BTK SH2 inhibitors represent the most selective BTK inhibitors identified to date

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

Targeting the SH2 domain via a prodrug modality represents a potential advantage to concentrate BTK SH2i compound intracellularly to achieve potent pathway inhibition

Primary human B cells (CD69) or TMD8 B cells (pERK) were stimulated with anti-IgM to initiate B cell receptor (BCR) signaling

BTK SH2i led to potent inhibition of both proximal SH2-dependent phosphorylation (pERK) and pro-inflammatory gene expression (CD69), phenocopying BTK TKIs **(Figure 4)**.

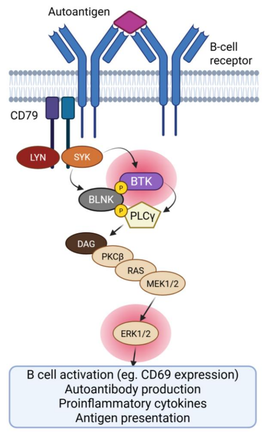
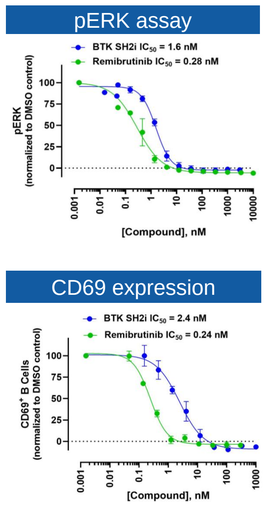


Figure 4. BTK SH2i block pERK signaling and downstream immune cell activation (B cell CD69 expression).



Following intravenous dosing in dogs, active BTK SH2i maintained durable intracellular exposures in target PBMCs while exposure of the prodrug was transient. BTK SH2i exposure in PBMCs enabled deep, durable, and dose-dependent target engagement **(Figure 5)**.

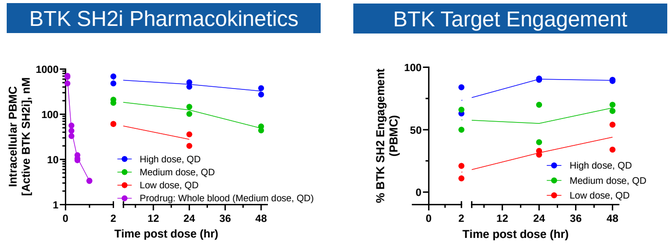
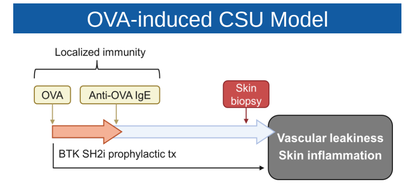


Figure 5. Recludix BTK SH2i achieves durable intracellular PK leading to prolonged target engagement in dog PBMCs following intravenous dosing.

This durable PK and target engagement profile is associated with dose-dependent reduction in skin inflammation in a mouse preclinical CSU model following single-dose prophylactic treatment **(Figure 6)**.



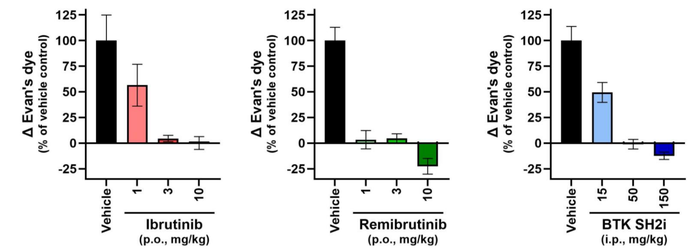


Figure 6. BTK SH2i reduce skin inflammation in a clinically-relevant model of CSU.

Conclusions

Recludix Pharma has generated the first potent and selective inhibitors of the BTK SH2 domain

Using a prodrug modality, BTK SH2i compounds achieve durable intracellular PK and target engagement profiles

Achieving durable pathway inhibition and improving known off-target selectivity may provide meaningful differentiation versus the BTK TKIs in current clinical development

Acknowledgements

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