Preclinical Characterization of BCX17725, a Potent Inhibitor of KLK5 and KLK14, for the Treatment of Netherton Syndrome

Poster ID
1047

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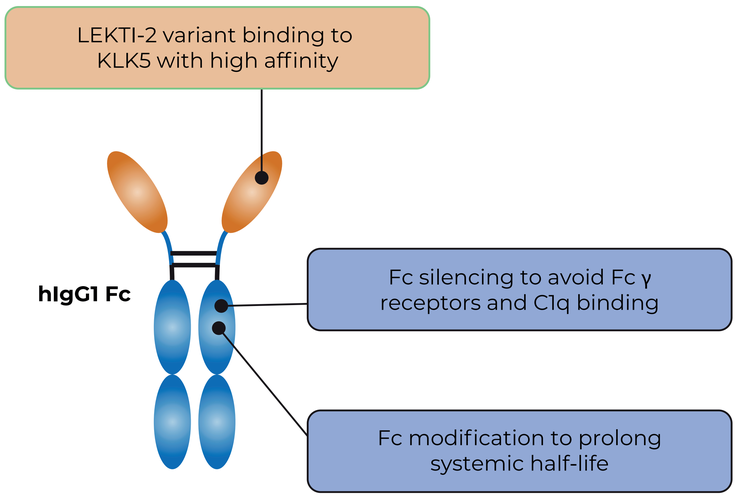
INTRODUCTION

- SPINK5-syndromic epidermal differentiation disorder (SPINK5-sEDD) or Netherton syndrome (NS) is a rare, severe, genetic disease caused by the loss of activity of the lympho-epithelial Kazal-type inhibitor (LEKTI), which leads to kallikrein-related peptidase 5 (KLK5)-initiated activation of the epidermal kallikrein (KLK) cascade.
- Unregulated activity of KLK proteolysis results in skin barrier dysfunction, chronic inflammation, and atopy.
- KLK5, KLK-related peptidase 7 (KLK7), and KLK-related peptidase 14 (KLK14) are the major KLKs in the pathogenesis of NS.
- Both KLK5 and KLK14 activate protease-activated receptor 2 (PAR2) and result in a proinflammatory response in NS.
- BCX17725, a novel recombinant fusion protein, is a potent inhibitor of KLK5 and KLK14 designed to help restore epidermal protease balance and improve skin barrier function in patients with NS.

Figure 1. Structure of BCX17725, a Potent Inhibitor of KLK5/14, in Development for the Treatment of Netherton Syndrome



C1q, complement component C1q; Fc, fragment crystallizable; hIgG1, human immunoglobulin G1.

OBJECTIVE

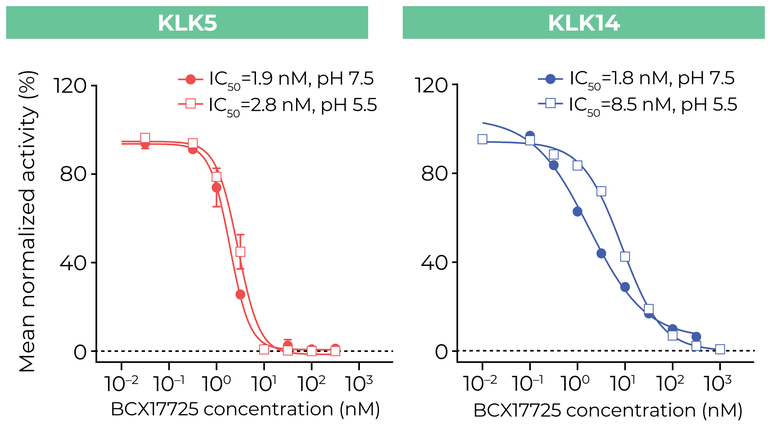
- To assess the potency of BCX17725 against KLK5- and KLK14-mediated activities.

METHODS

- KLK5 and KLK14 enzymatic activities were measured using a Val-Pro-Arg fluorescent peptide substrate (7-amino-4-methylcoumarin) under pH 7.5 and 5.5 conditions.
- Binding affinities of BCX17725 for KLK5 and KLK14 were evaluated using surface plasmon resonance (SPR).
- KLK5-mediated cleavage of human desmoglein-1 (DSG-1) was assessed by Western blot.
- KLK5-mediated and PAR2-mediated interleukin-8 (IL-8) induction in A549 lung epithelial cells was measured by enzyme-linked immunosorbent assay (ELISA).

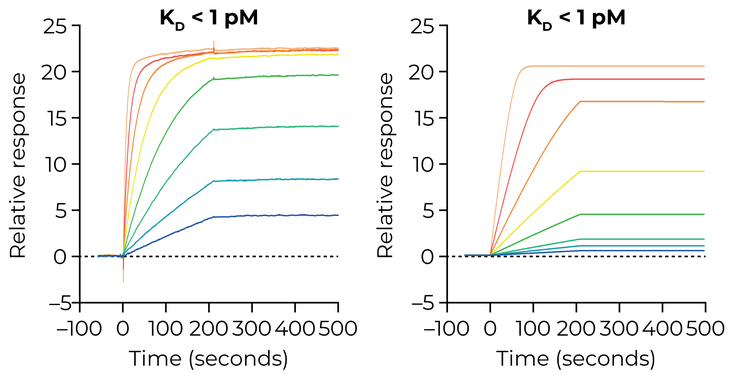
RESULTS

Figure 2. BCX17725 Potently Inhibited the Enzymatic Activity of Human KLK5 and KLK14



Error bars show standard deviations.
IC_{50}, half-maximal inhibitory concentration.

Figure 3. BCX17725 has Very High Binding Affinity to KLK5. SPR Sensorgram for BCX17725 Binding to KLK5 at pH 7.5 (left) and pH 5.5 (right)



The different colors represent the KLK5 concentration series used in the injection.
K_D, equilibrium dissociation constant.

Table 1. Binding Affinity of BCX17725 for KLK5 and KLK14 at pH 7.5

	Binding parameters		
	k_a (1/[M*s])	k_d (1/s)	K_D (pM)
KLK5	1.29E+07	<1.0E−05	<1
KLK14	1.13E+09	4.39E−03	4.52

k_a, association rate constant; k_d, dissociation rate constant.

Table 2. Selectivity of BCX17725: Inhibitory Effect of BCX17725 Against Human Serine Proteases

Enzyme	IC_{50}, nM	Fold reduction in potency relative to IC_{50} of KLK5
C1s	>1000	>455
Plasmin	>1000	>455
Thrombin	>1000	>455
APC	>1000	>455
tPA	>1000	>455
Trypsin	311	183
FXa	>1000	>455
FXIIa	>1000	>455

APC, activated protein C; C1s, complement component 1s; F, factor; tPA, tissue-type plasminogen activator.

Figure 4. BCX17725 Inhibited Human KLK5-Mediated Proteolytic Degradation of Human DSG-1

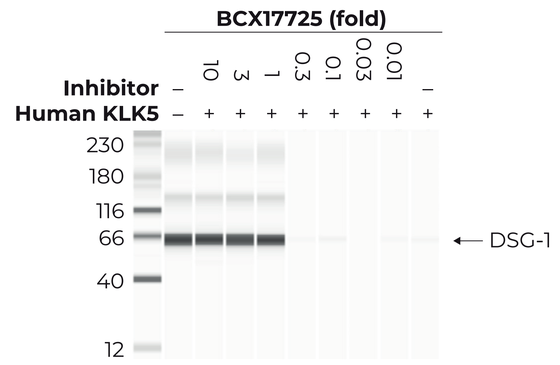
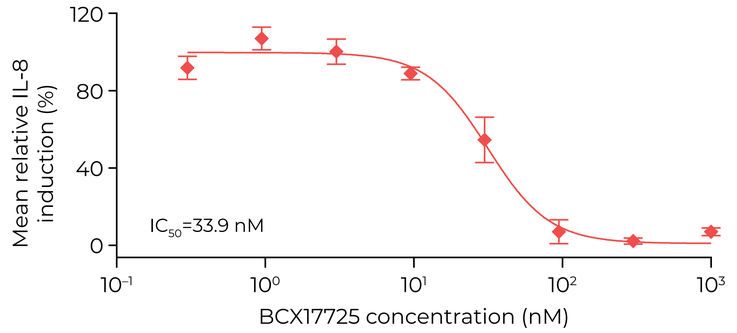
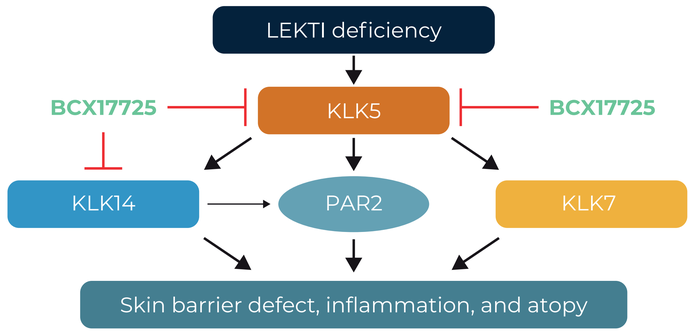


Figure 5. BCX17725 Inhibition of KLK5-Induced IL-8 Secretion



Error bars show standard deviations. A549 epithelial cells were incubated with KLK5 with or without BCX17725. IL-8 levels were measured by ELISA.

Figure 6. BCX17725 Mechanism of Action



CONCLUSIONS

1. BCX17725 binds to KLK5 and KLK14 with high affinity and potently inhibits in vitro activities of KLK5 and KLK14.
2. BCX17725 potently inhibits KLK5-mediated and PAR2-mediated cytokine release in cell-based study.
3. These data support clinical development of BCX17725 for the treatment of NS.

Poster presented at the 83rd Society for Investigative Dermatology (SID) Annual Meeting • May 13–16, 2026 • Chicago, IL, USA

Funded by BioCryst Pharmaceuticals, Inc.