BGB-16673 (TACABRUTIDEG), A POTENT BTK DEGRADER IN HUMAN BLOOD AND CANCER CELL LINES, SHOWS HIGH SELECTIVITY IN BOTH PROTEOMICS AND KINOME PANEL ANALYSES

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INTRODUCTION

Targeted protein degradation is a therapeutic modality with potential to address unmet medical needs[1]. BTK degraders such as BGB-16673 (Tacabrutideg) and NX-5948, which offer strategies to overcome limitations of BTK inhibitors, are at late-stage of clinical development. However, due to the composite pharmacology of degraders, evaluating compound selectivity—which is critical for safety assessment and compound mechanism understanding—in systems that may enable assessment of patient selectivity at clinically relevant exposures remains challenging. High plasma protein binding (PPB) [2] of the compounds further complicates translation, as drug levels in standard culture media often difficult to reflect human exposure.

AIMS

- To evaluate the potency of BGB-16673 and NX-5948 in human lymphoma cell lines and human whole blood.
- To profile proteome-wide degradation selectivity across blood cell types under whole-blood treatment at 37°C to mitigate PPB confounding and mimic the human condition.
- To assess kinase inhibition selectivity using an in vitro kinome panel.

METHODS

- BTK degradation in human whole blood was quantified by ELISA, in CD20+ B cells of whole blood by flow cytometry.
- Proliferation inhibition in TMD8 cells was measured by CellTiter Glo assay.
- Human whole blood was incubated with compounds for 16 hours at 37°C in whole blood; B cells, T cells, neutrophils, platelets were then isolated for mass spectrometry.
- Kinome selectivity at 25nM compound concentration was assessed by a commercial panel.

RESULTS

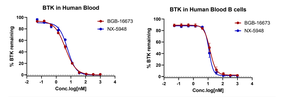
Figure 1. BGB-16673 showed single-digit nano molar potency of BTK degradation in lymphoma cancer cell lines and human blood

A.

Cancer cells		BGB-16673	NX-5948
TMD8	DC50 (nM)	0.57	0.56
	DC90 (nM)	3.40	2.57
TMD8	GI50(nM)	4.06	5.92
	GI90(nM)	4.72	6.78

DC50, 50% BTK degradation; DC90% 90% BTK degradation; GI50, 50% cell growth inhibition; GI90, 90% cell growth inhibition

B.

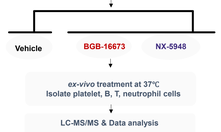


BTK degradation		BGB-16673	NX-5948
Human whole blood	DC50 (nM)	4.19	5.91
	DC90 (nM)	26.3	25.4
Human B cells in whole blood	DC50 (nM)	13.6	11.7
	DC90 (nM)	38.0	24.4

The potency of BTK degraders in different cells. ***A.*** *A table of the number of DC50, GI50 for BGB-16673 and NX-5948 in cancer cell line TMD8.* ***B.*** *The degradation curve of BGB-16673 and NX-5948 in human whole blood, and in B cells of whole blood.*

Figure 2. Workflow of proteomics analysis experiment in human whole blood samples to examine degradation selectivity

A. Workflow



- BTK degrader was added to human whole blood to minimize PPB-related confounding and better reflect physiological conditions compared with PBMC.
- Samples were incubated for 16 hours at physiologic temperature to allow maximal BTK degradation

B. Compound concentrations and cell populations

Compounds	Doses	Rationale
BGB-16673	• 160nM	• A Cmax-related concentration for BGB-16673 at 200mg QD in patients
	• 250nM	• 10x DC90 for BTK degraders in human whole blood
NX-5948	• 100nM	• A concentration potentially related to exposure at 600mg in patients
	• 160nM	• Same concentration comparison
	• 250nM	• 10x DC90 of BTK degraders in human whole blood

- Cells related to indications (B cells), immune therapy combinations (T cells), or potential AEs, e.g. infection (neutrophils and platelets) were chosen for proteomics analysis to examine its selectivity.
- Isolation avoids false-positive or false-negative signals caused by differences in whole-blood composition between individuals.

Study design of mass spectrometry experiment profiling the degradation selectivity of protein degraders in human whole blood. ***A.*** *Workflow of experiments. Human whole blood from healthy donors (N=6) were incubated with BTK degraders, then different cell populations was isolated for LC-MS/MS analysis.* ***B.*** *Concentrations of BGB-16673 and NX-5948 used in experiments. DC90 was shown in Fig 1B.*

CONCLUSIONS

BGB-16673 is a potent BTK degrader with high selectivity across key blood cell types by proteomic profiling. Both degraders reduce TEC in platelets, while BGB-16673 shows markedly higher selectivity of kinase inhibitions than NX-5948. The clinical relevance of these selectivity profiles warrants further validation.

REFERENCES

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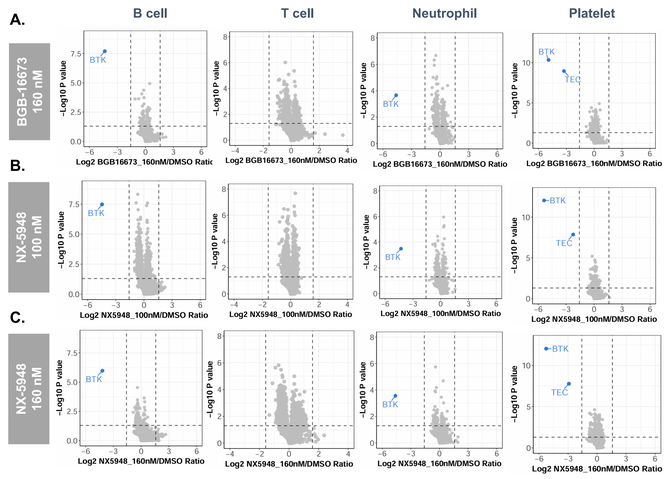
[2] Singh, S. and Srivastava, P. (2024) "Targeted Protein Degraders- The Druggability Perspective," Journal of Pharmaceutical Sciences, 113(3), pp. 539–554. Available at: https://doi.org/10.1016/j.xphs.2023.10.023.

[3] https://recludixpharma.com/wp-content/uploads/2025/06/FASEBJune2025Final.pdf

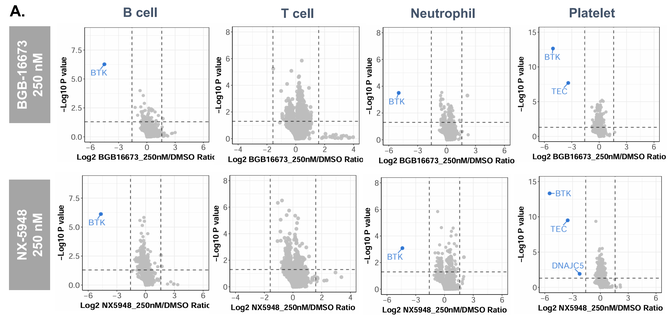
Figure 3. Proteomics analysis in human blood demonstrated that BGB-16673 is a highly selective BTK degrader at clinically relevant concentrations



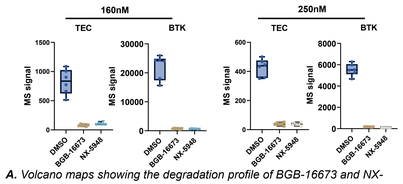
Volcano maps showing the degradation profile of BGB-16673 and NX-5948 in B cells, T cells, neutrophiles, and platelets in whole blood under clinically relevant concentrations based on data from 6 healthy donors. Foldchange=3 (log2 value is ~1.58), P=0.05 was highlighted by dashed lines in X and Y axis, respectively. Concentrations was chosen based on rationale in ***Figure 2****.*

A. *BGB-16673 showed high selectivity at 160nM across B cell, T cell, neutrophil, and platelets: BGB-16673 induced significant degradation of BTK in B cells and neutrophils, no other off target degradation was observed. Consistently, in T cells which do not express BTK, no significant degradation of any protein could be identified, supporting BGB-16673's high selectivity. In platelets, in addition to BTK degradation, one off target degradation of TEC protein was observed.*
B-C. *NX-5948 showed high selectivity at 100nM & 160nM in B cells, T cells, and neutrophils. Off target degradation of TEC protein was also observed in platelets in both conditions.*

Figure 4. Proteomics analysis in human blood showed that BGB-16673 remains to be a selective BTK degrader at higher concentration (at 10x DC90)



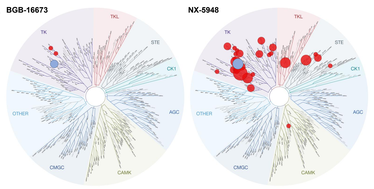
B. Degradation of platelet BTK and TEC proteins in whole blood



A. *Volcano maps showing the degradation profile of BGB-16673 and NX-5948 in B cells, T cells, neutrophiles, and platelets in whole blood at 250nM (10× whole-blood DC90) based on data from 6 healthy donors. Foldchange=3 (log2 value is ~1.58), P=0.05 was highlighted by dashed lines in X and Y axis, respectively. BGB-16673 and NX-5948 presented high selectivity in B cells, T cell, and neutrophils. TEC is an off-target degradation in platelets.* ***B.*** *Box plot showing TEC & BTK degradation of degraders in platelets in whole blood. Bloods from different 6 donors were used for 160nM and 250nM treatment.*

Figure 5. BGB-16673 presented less off-target inhibition in kinome profiling under concentration achieve 90% degradation in human whole blood

A. BGB-16673 NX-5948



B.

CMPDs	NX-5948 25nM		BGB-16673 25nM	
Inhibition%	Off-target number	Off-target percent (%)	Off-target number	Off-target percent (%)
≥90	7	1.8	0	0
<90 and ≥80	12	3.1	0	0
<80 and ≥70	9	2.3	2	0.5

DC90(25nM) with 1uM ATP by Reaction biology

Kinome selectivity of BGB-16673 and NX-5948. The BTK binding part of BTK degraders binds to BTK kinase domain, indicating potential kinase inhibition activity. To assess kinase selectivity, the two BTK degraders were profiled across a panel of 383 kinases at Reaction Biology. Given the high PPB of BTK degraders, a concentration that achieve 90% BTK degradation in human whole blood was considered more clinically relevant and therefore used for kinome selectivity profiling. ***A.*** *A circular representation of the kinase family tree based on kinase domain sequence. The diameter of the red circle correlated with the affinity with which the degraders inhibit the kinase. Consistent with published data [3], NX-5948 showed many off-target hits in this profiling; while BGB-16673 showed high selectivity.* ***B.*** *Table summary of number of kinases with over 70% inhibition of each compound in* ***Fig A****.*