Polymed's PROTAC Platform: Focus on IRAK4 (HPB-143)

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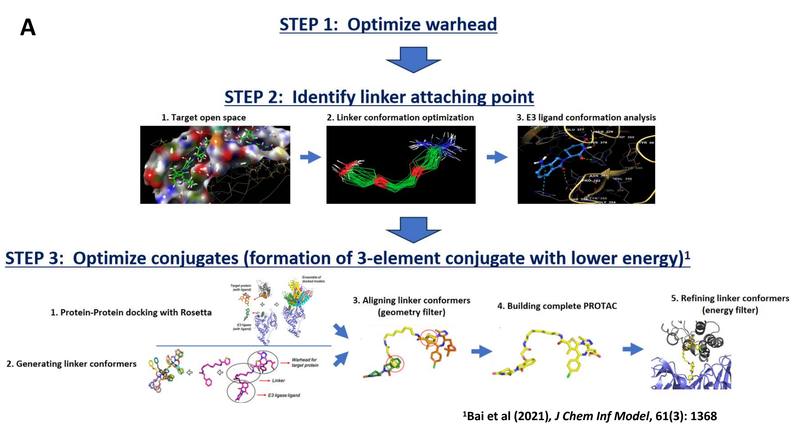
Abstract

PROTAC represents a novel modality in drug discovery by degrading disease-causing proteins, overcoming the limitations of traditional inhibitors that only block enzyme activity. This technology is particularly effective against some "undruggable" targets such as scaffold proteins, protein-protein interaction, transcription factors, enzymes with shallow binding pockets, and proteins prone to mutations that lead to drug resistance. Polymed utilizes a proprietary linker technology, combining medchem and AIDD algorithm to design PROTAC molecules with high potency and excellent oral bioavailability. Proteomics Q-tagging Technology was also applied to evaluate ubiquitination in the process. The company has created potent PROTAC degraders targeting IRAK4, KRAS and EGFR for the treatment of autoimmune disease and cancer.

HPB-143 is an IRAK4 PROTAC with excellent oral bioavailability (49% in mice) and a clean cardiac safety profile (hERG IC_{50} > 10 uM). HPB-143 demonstrated efficacy in multiple preclinical models of inflammatory and autoimmune diseases. Polymed has completed all CMC work and GLP tox studies of HPB-143 and submitted the IND application to the FDA (September 2024).

PROTAC and DAC platforms



1. Optimal ternary complex interactions
2. Optimal oral ADME /PK properties
3. Library of >200 linkers

Figure A. Proprietary AI/CADD algorithm enables rapid design of effective PROTAC drugs

Figure B. Polymed linker technology

Figure C. Degrader antibody conjugates

Protacs targeting IRAK4, KRAS and EGFR have 1-3 nM DC50 and excellent PK profile

Compound ID	Target	Cell lines	DC_{50} (nM)	Dmax (%)	F (%)
Protac HPB-143	IRAK4	hPBMC	1.8	100	49
Protac 2	KRAS	AsPC-1	2.7	90	8
Protac 3	EGFR	BaF3-FL-EGFR-DTC	1.2	99	35
DAC 1	KRAS	GP2D	1.1	99	NA

NA: Not available.

PROTAC HPB-143 has excellent PK profiles

Compound ID		KT474	HPB-02-143		
Species		Mice	Mice	Rat	Beagle Dog*
PO (10mpk)	C_{max} (ng/mL)	365	3659	2160	1117
	T_{max} (h)	0.5	4.0	8.1	6.0
	$T_{1/2}$ (h)	2.53	4.37	7.2	15.2
	$AUC_{(0-t)}$ (h.ng/mL)	2285	40655	39784	22937
	F (%)	15	49	32	43

* 20 mpk

HPB-143 is efficacious in oxazolone-induced atopic dermatitis model

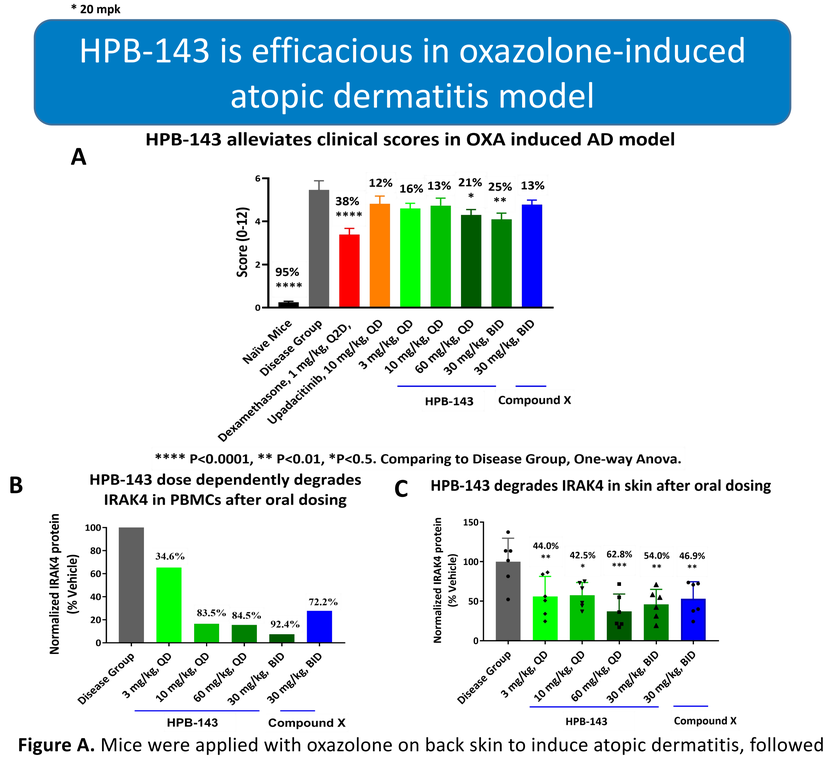


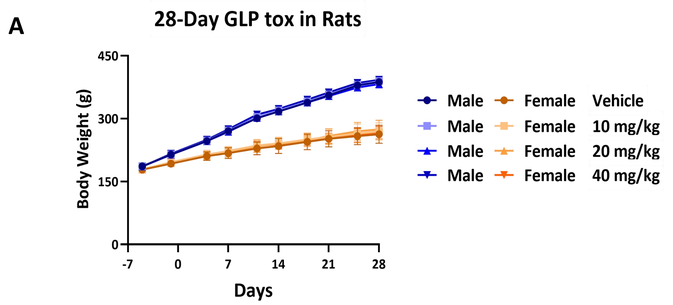
Figure A. Mice were applied with oxazolone on back skin to induce atopic dermatitis, followed by oral dosing of HPB-143, KT-474 or positive controls. Clinical score was calculated based on skin erosion, thickness, reddening and scaling.

Figure B & C. Degradation of IRAK4 in PBMCs and skin was also evaluated.

Compound X respresents a drug candidate that is currently in Phase II clinical trials.

HPB-143 has excellent safety profile

Genotoxicity	Mutagenicity Test	No mutation at up to 100 µg/mL.
	Chromosomal Aberration Study	No genotoxicity at up to 100 µg.
	Micronucleus Study	Negative at up to 2000 mg/kg.
Safety Pharmacology	Effect on Currents in hERG Potassium Channel	No inhibition at up to 17.81 µmol/L.
	Effects on Central Nervous System Functions	No effects at up to 40 mg/kg.
	Effects on Cardiovascular and Respiratory Functions	No effects.



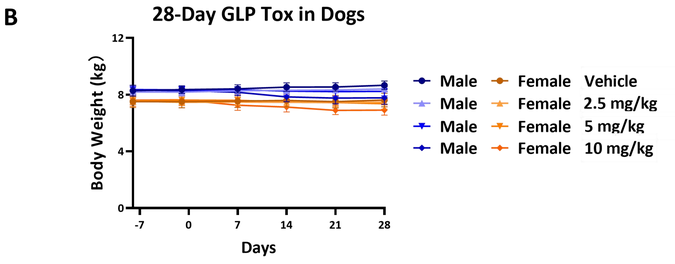


Figure A & B. No adverse effects observed in Rats (NOAEL: 40 mg/kg) and Dogs (NOAEL: 5 mg/kg). No abnormal in body weight, food consumption in Rats and Dogs.

Summary

- Leveraging AI, structural biology and proteomics, Polymed addresses "undrugg-able" targets by developing bifunctional compounds, such as protein degraders
- HPB-143 potently and dose-dependently reduces targeted protein levels *in Vitro* and *in Vivo* with good efficacy
- Manufacturing of drug substance and drug product were well controlled. Oral tablets as clinical dosage form showed excellent oral PK properties in preclinical studies. Both drug substance and drug product demonstrate good stability with current stability data
- HPB-143 has excellent safety profiles in GLP Genotoxicity, safety pharmacology and toxicity studies
- **FDA IND application of HPB-143 was submitted in September 2024**

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