Abstract #5497

Preclinical characterization of FHT-171, a first-in-class degrader targeting CREB-binding protein (CBP) in CBP-dependent solid tumors

Darshan Sappal, Benjamin Adams, Ketaki Adhikari, Hafiz Ahmad, Brandon Antonakos, Kidochukwu Atube, Wesley Austin, Steve Bellon, Breanna Bullock, Mike Collins, Julie Di Bernardo, Thomas Dixon, Danette Daniels, Claudia Dominici, Brian Ethell, Katharine Feldman, Md Imran Hossain, Dave Lahr, Laura La Bonte, Michael Lehrke, Mei Yun Lin, David Mayhew, Karolina Mizeracka, Paige Monsen, Solymar Negretti, John Pulice, Abira Ramakrishnan, Shawn Schiller, Samantha Schultz, Saurabh Sewak, Gromek Smolen, Nihan Ucisik, Jessica Wan, Grace Werosta, Molly Wilson, Elizabeth Wittenborn, Xiaohuan Wu, Qianhe Zhou, Mark Zimmerman

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ABSTRACT

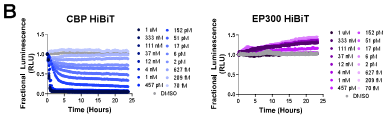
The paralog lysine acetyltransferases CREB-binding protein (CBP) and E1A-binding protein P300 (EP300) function as transcriptional coactivators that regulate diverse cellular programs. Functional screens have revealed a bidirectional synthetic relationship between these two paralogs in tumor cell biology. This synthetic lethal relationship offers a therapeutic opportunity in selectively targeting CBP in *EP300*-mutant as well as other CBP-dependent cancers. Herein, we present a comprehensive preclinical evaluation for a first-in-class, selective CREBBP (CBP) degrader, FHT-171, designed to target transcriptional coactivator dependencies in solid tumors. Through a series of in vitro and in vivo studies, we characterize the compound's biochemical selectivity, cellular degradation kinetics, transcriptional impacts, antitumor efficacy and tolerability across multiple solid tumor models. These findings provide mechanistic and non-clinical translational insight into the therapeutic potential of CBP degradation and support further development of this novel modality for the treatment of CBP-dependent malignancies.

Biochemical and cellular characterization of FHT-171

A

		FHT-171
On-Target	U2OS CBP uDC$_{20}$ (nM) [D$_{max}$,%]	0,028 [94]
	MCF7 CBP uDC$_{20}$ (3 hr, nM)	0,025
Off-Target	EP300 / BRD4 TR-FRET IC$_{50}$ (µM)	0,11 / 7,2
	U2OS EP300 uDC$_{20}$ (µM) [D$_{max}$,%]	> 2,1 [0]
	BRD4 uDC$_{20}$ (µM) [D$_{max}$,%]	> 2,1 [40]
ADME	LMS (m / r / d / mk / h) (CL$_{int}$, µL/min/mg)	4 / 0 / 3 / 27 / 5
	Pred, Hu (CL$_{int}$, mL/min/Kg) (Allometry & SSS range)	3 - 5
	IV CL (mL/min/Kg)	32 / 16 / 7 / 14
	T$_{1/2}$ (h) [m / r / d / mk]	3,5 / 1,4 / 4,6 / 1,2
	Vdss (L / Kg)	3,3 / 0,3 / 0,3 / 0,3
In Vitro Safety	hERG, TDI, Cyp Inhib, Cyp Induc, SafetyScan47, BromoMAX	No Identified Concerns

B



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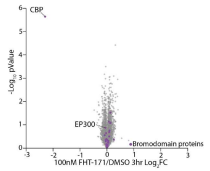

Figure 1. A) Biochemical and cellular characterization of FHT-171 **B)** Dose-response kinetic profiling of CBP degrader FHT-171 confirms potency and selectivity of CBP degradation over EP300. **C)** Proteomics demonstrates selectivity of FHT-171 for CBP over other proteins, including those containing bromodomains.

DepMap suggest indications for CBP degraders beyond *EP300*-mutant cancers

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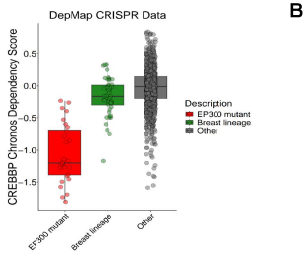

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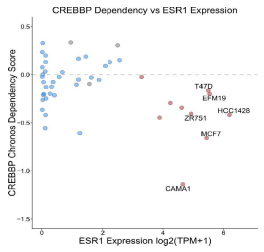

Figure 2. A) CBP dependency identified by DepMap CRISPR screening extends beyond EP300-mutant cell lines **B)** ER+ breast cancer cell lines demonstrate sensitivity to CBP loss.

FHT-171 demonstrates activity in ER+ breast cancer

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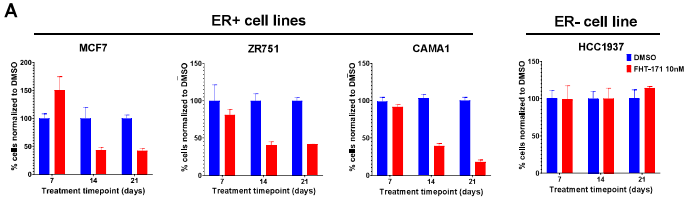

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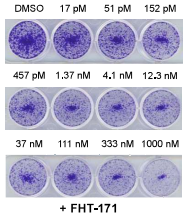

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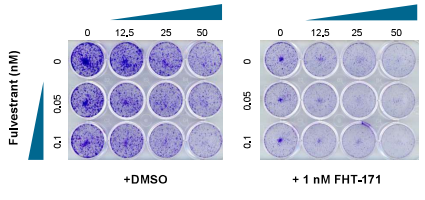

Figure 3. A) Single agent antiproliferative activity observed in ER+ cancer cell lines treated in a long-term assay with FHT-171 **B)** Crystal violet staining of MCF7 cell line colonies after 14 days of treatment with FHT-171 **C)** MCF7 cell line colonies after 14 days of treatment with abemaciclib, fulvestrant, and DMSO or 1 nM FHT-171 indicates combinatorial benefit of triplet therapy.

FHT-171 regulates ER and ER target genes

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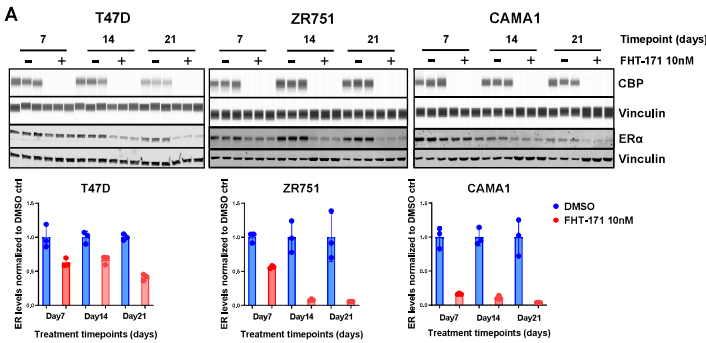

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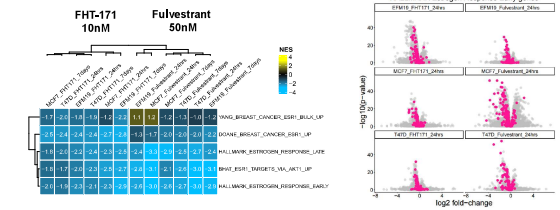

Figure 4. A) Long-term treatment with FHT-171 affects ER protein levels **B)** FHT-171 treatment causes downregulation of ER target genes.

FHT-171 demonstrates efficacy in ER+ PDX models

A

PDX model	Patient segment	%TGI with 10mpk FHT-171
ST4680D	ESR1m	104%
ST3164B	ESR1 fusion	60%
ST4887B	ESR1 WT	59%
ST941C	ESR1m	51%
ST5400	ESR1 WT	47%
ST3932	ESR1 WT	39%

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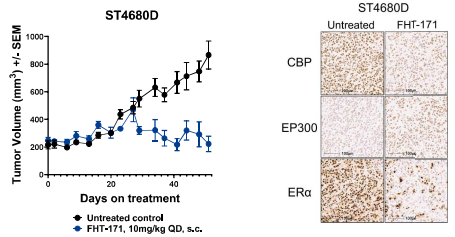

Figure 5. A) FHT-171 shows single agent activity in multiple CDK4/6i resistant CDX/PDX models **B)** IHC analysis indicates selective targeting of CBP over EP300 and modulation of ER levels.

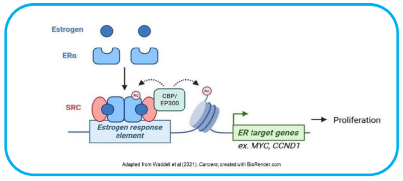

Figure 6. Model showing CBP/EP300 as essential coactivators of the ER complex. Through their recruitment to ER-bound enhancers, they acetylate histones and ER-associated proteins, stabilize transcriptional complexes, and drive ER target gene transcription.

CONCLUSIONS

- We report the identification and preclinical characterization of FHT-171, a highly potent and selective degrader of CBP.
- FHT-171 exhibits single agent antiproliferative activity and enhanced activity in combination with Abemaciclib and Fulvestrant in ER+ breast cancer cell lines.
- FHT-171 treatment downregulates ER protein levels and ER target gene expression across multiple ER+ breast cancer cell lines.
- FHT-171 retains selectivity for CBP and delivers single agent efficacy across CDK4/6i and endocrine therapy resistant CDX and PDX models.