#5780 Discovery of first-in-class potent and selective oral CCNE1 molecule glues that show robust anti-tumor activities and better safety profile

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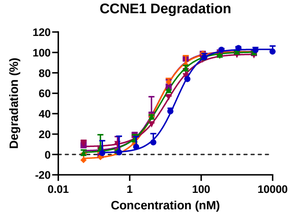
Introduction

- Cyclin E1 (CCNE1) is a key cell cycle regulatory protein and binds to cyclin-dependent kinase 2 (CDK2), forming a CCNE1-CDK2 complex, which is essential for driving the cell cycle progression to S-phase for subsequent DNA replication.
- Amplification of the CCNE1 locus on chromosome 19q12 is prevalent in multiple tumor types, particularly in breast cancer, high-grade serous ovarian cancer, uterine tumors, and gastro-esophageal cancers. In breast cancer, amplification of CCNE1 is a potential cause of resistance to CDK4/6 inhibitor. CCNE1 amplification may also confer resistance to chemotherapy and is associated with poor overall survival. Therefore, there is a significant unmet medical need for tumors with CCNE1 amplification. Compared with CDK2 inhibitors, CCNE1 molecular glues exhibit better selectivity, thereby reducing the adverse effects caused by CDK2 inhibitors in clinical trials.
- Here, we report that CCNE1 molecular glues potently inhibit CCNE1-amplified cells both *in vitro* & *in vivo* and show better selectivity and superior safety relative to CDK2 inhibitor..

CCNE1 Degraders Display Potent Degradation Activity



	ATH-007	ATH-008	ATH-009	ATH-010	ATH-011
DC_{50} (nM)	18	7	10	6	6

Fig. 1 CCNE1 degraders potently degrade CCNE1 and achieves complete protein degradation (D_{max} of ~100%). Alpha ELISA was employed to quantify CCNE1 levels in MKN1 cells after 24 hours of compound incubation.

CCNE1 Degrader Shows Better Selectivity

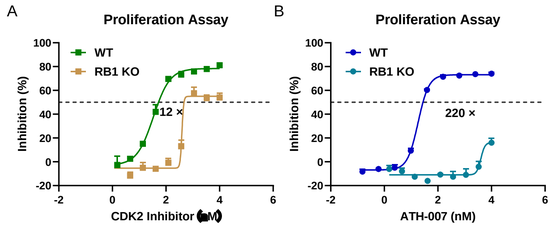


Fig. 2 In contrast to CDK2 inhibitor, ATH-007 displays markedly improved selectivity. The antiproliferative activity of (A) CDK2 inhibitor and (B) ATH-007 in wild-type (WT) and RB1 knockout (RB1 KO) cells was assessed using the CellTiter-Glo Kit.

CCNE1 Degrader Shows Excellent Degradation Selectivity

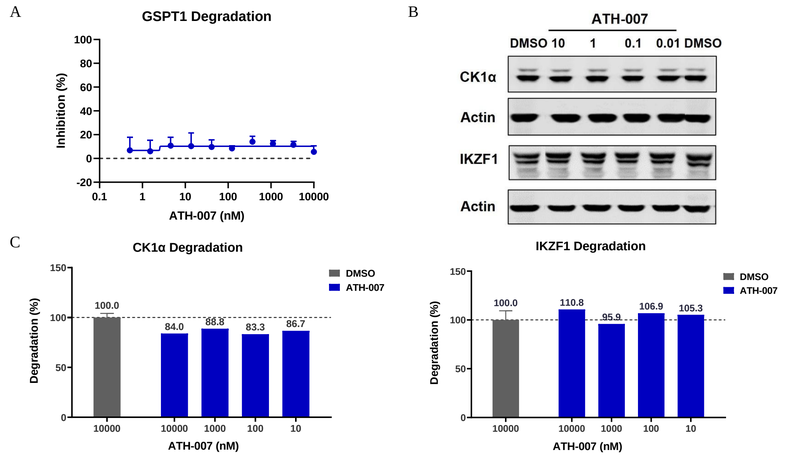


Fig. 3 ATH-007 exhibits excellent degradation selectivity. (A) The HiBiT assay was used to assess the activity of ATH-007 in HEK293 GSPT1 HiBiT KI cells. (B-C) The degradation activity of ATH-007 against CK1α and IKZF1 was measured in OCI-LY10 cells by Western blot.

CCNE1 Degraders Inhibit CCNE1^{amp} Cells

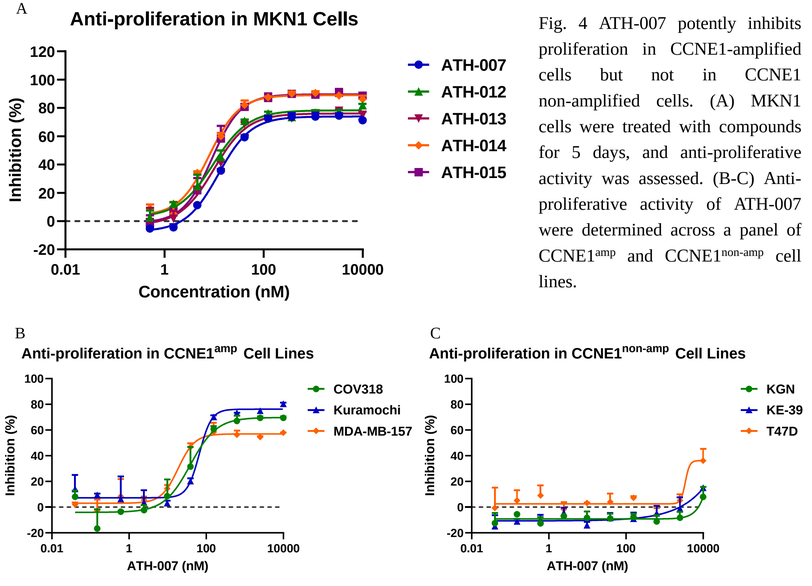


Fig. 4 ATH-007 potently inhibits proliferation in CCNE1-amplified cells but not in CCNE1 non-amplified cells. (A) MKN1 cells were treated with compounds for 5 days, and anti-proliferative activity was assessed. (B-C) Anti-proliferative activity of ATH-007 were determined across a panel of CCNE1^{amp} and CCNE1$^{non\text{-}amp}$ cell lines.

CCNE1 Degrader Shows Tumor Suppression Activity

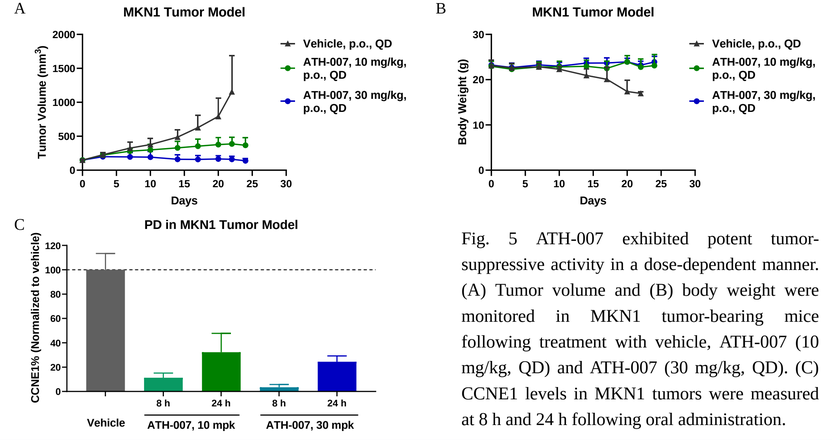


Fig. 5 ATH-007 exhibited potent tumor-suppressive activity in a dose-dependent manner. (A) Tumor volume and (B) body weight were monitored in MKN1 tumor-bearing mice following treatment with vehicle, ATH-007 (10 mg/kg, QD) and ATH-007 (30 mg/kg, QD). (C) CCNE1 levels in MKN1 tumors were measured at 8 h and 24 h following oral administration.

CCNE1 Degrader Shows Negligible Hematological Toxicity

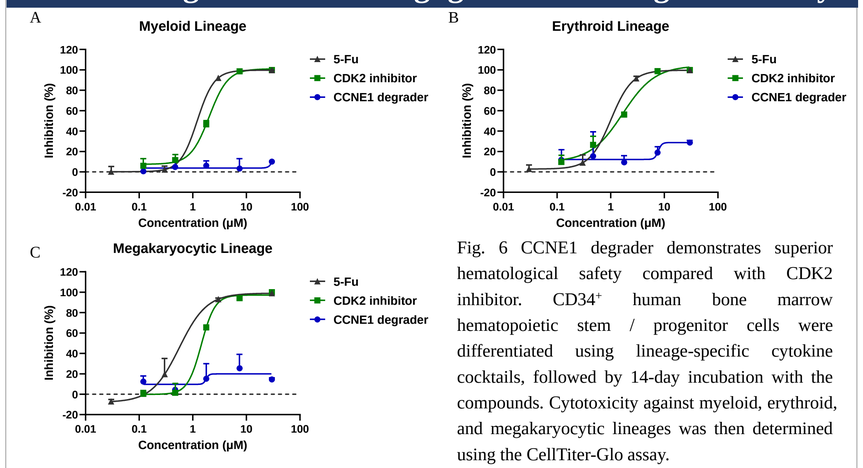


Fig. 6 CCNE1 degrader demonstrates superior hematological safety compared with CDK2 inhibitor. CD34^{+} human bone marrow hematopoietic stem / progenitor cells were differentiated using lineage-specific cytokine cocktails, followed by 14-day incubation with the compounds. Cytotoxicity against myeloid, erythroid, and megakaryocytic lineages was then determined using the CellTiter-Glo assay.

Conclusions

1. CCNE1 molecular glues potently inhibit CCNE1-amplified cells both *in vitro* & *in vivo*.
2. Compared to CDK2 inhibitor, CCNE1 molecular glue shows better selectivity over non-CCNE1-amplified cells.
3. In *in vitro* hematotoxicity assay, CCNE1 molecular glue shows superior safety relative to CDK2 inhibitor.
4. Compared with ATH-007, PCC candidate shows better degradation activity and PK properties.
5. IND enabling study will be initiated soon.

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