CID-078, a First-in-Class Oral Macrocycle Cyclin A/B-RxL Inhibitor, Demonstrates Anti-Tumor Activity in E2F-driven Cancers

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Abstract Number PB-515

BACKGROUND

- The cyclin-dependent kinase (CDK)-RB-E2F axis forms the core transcriptional machinery driving cell cycle progression. Alterations in *RB1* or other pathway members occur in many cancers resulting in heightened oncogenic E2F activity. The activity of E2F is regulated by RxL-mediated binding to the hydrophobic patch (HP) or RxL binding site of Cyclin A; blocking this interaction results in hyperactivation of E2F and synthetic lethality in E2F-addicated tumors.
- While mechanistically differentiated and potentially more selective than blocking CDK activity (e.g., CDK2 or CDK4 inhibitors), the cyclin A/E2F RxL interaction was deemed undruggable.
- Leveraging our MXMO™ platform, we discovered CID-078, a passively permeable, selective, and orally bioavailable macrocycle with dual cyclin A/B RxL inhibiting activity that demonstrates efficacy in multiple E2F-driven cancer indications.

Figure 1. The MXMO™ drug discovery engine integrates computational and synthetic platforms to rapidly generate macrocycles that can be administered orally

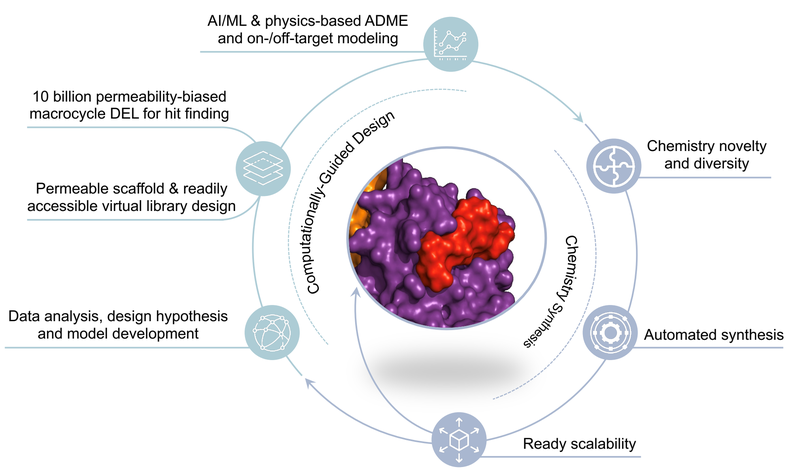
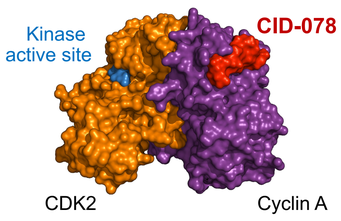
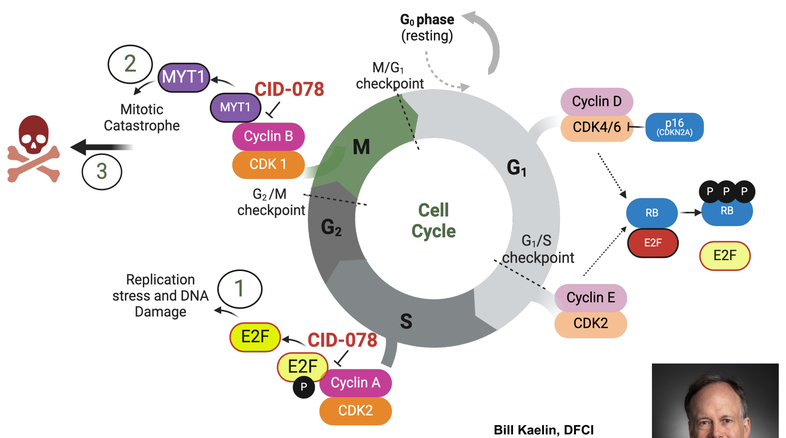


Figure 2. MXMO™ has enabled the discovery of CID-078, a First-in-Class Oral Macrocycle Cyclin A/B-RxL Inhibitor



CID-078:

- Binds "undruggable" hydrophobic patch (HP)/RxL binding site in Cyclins A and B
- Blocks the interaction of E2F1 with Cyclin A-Cdk2 and Myt1 with Cyclin B-Cdk1
- Leads to DNA damage and mitotic catastrophe in E2F high tumors (e.g., SCLC, NSCLC, TNBC)
- Differentiated binding site and MoA from CDK inhibitors



Bill Kaelin, DFCI
First demonstrated the therapeutic potential of targeting cyclins with RxL peptides

Figure 3. CID-078 has activity across many tumor models

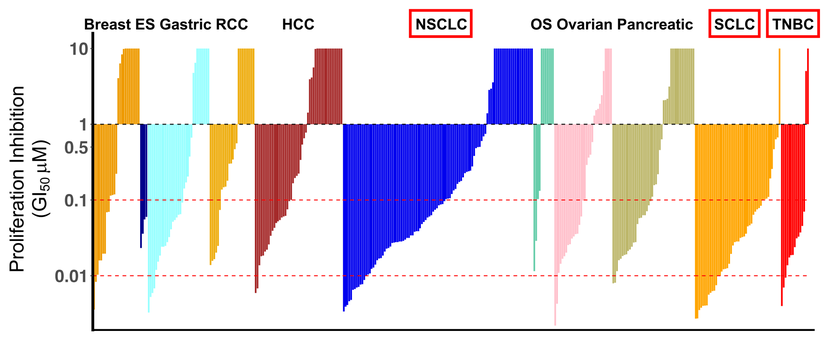


Figure 3. GI_{50} waterfall plots in response to CID-078. CID-078 was profiled for anti-proliferation activity in a broad panel of cell lines representing various solid tumor indications. Cell lines were exposed to CID-078 for 4-8 days depending on length of time required for at least two cell doublings to occur. Cell growth inhibition was determined by Cell Titer Glo assay. ES, Ewing sarcoma; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; OS, osteosarcoma; SCLC, small cell lung cancer; TNBC, triple negative breast cancer

Results

Figure 4. SCLC: CID-078 activity is associated with higher expression of E2F targets and the G2M checkpoint pathway

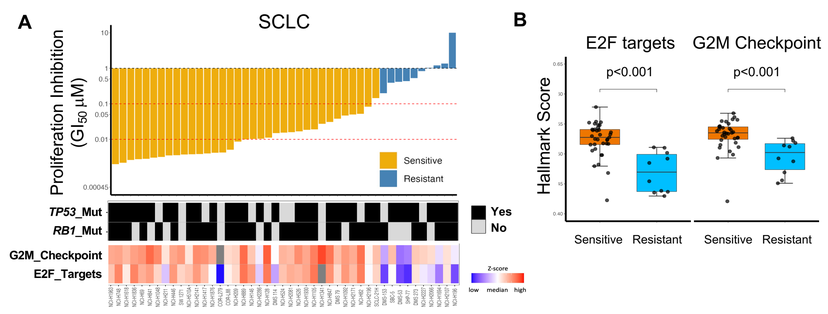
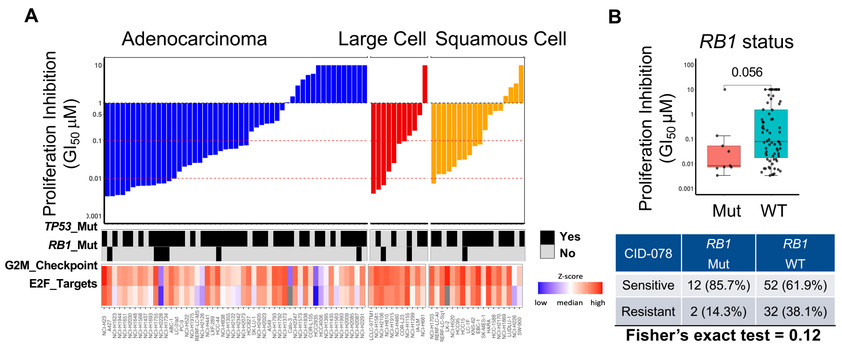


Figure 4. (A) Waterfall plots of sensitivity (GI_{50}), genomic alteration status of *TP53* and *RB1*, and heatmaps of E2F targets and G2M checkpoint hallmark pathways Z-scores of 45 SCLC cell lines tested with CID-078. **(B)** E2F targets and G2M checkpoint hallmark pathway scores were associated with sensitivity to CID-078 in SCLC cell lines. Sensitivity is defined as GI_{50} < 300 nM. P-values are shown and calculated by the Wilcoxon rank sum exact test.

Figure 5. NSCLC: CID-078 activity trends with *RB1* status



CID-078	*RB1* Mut	*RB1* WT
Sensitive	12 (85.7%)	52 (61.9%)
Resistant	2 (14.3%)	32 (38.1%)

Fisher's exact test = 0.12

Figure 5. (A) Waterfall plots of sensitivity (GI_{50}), genomic alteration status of *TP53* and *RB1*, and heatmaps of E2F targets and G2M checkpoint hallmark pathways Z-scores of 98 NSCLC cell lines tested with CID-078. **(B)** *RB1* status based on DNA alterations trended with sensitivity to CID-078 in NSCLC cell lines. P-values are shown and calculated by the Mann-Whitney or Fisher's exact test.

Figure 6. Breast Cancer: TNBC shows higher expression of E2F targets and sensitivity to CID-078

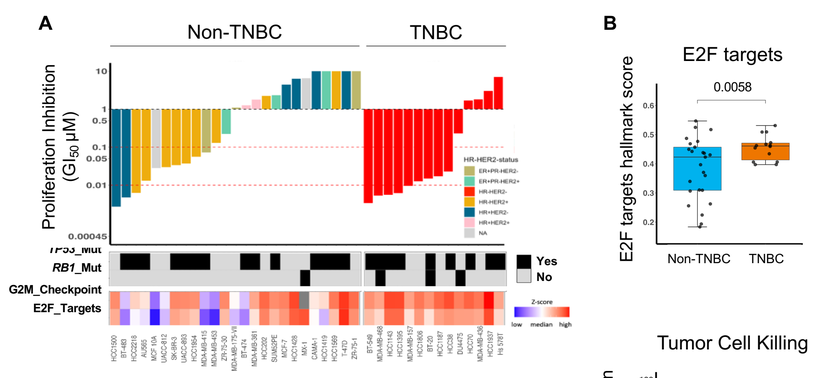
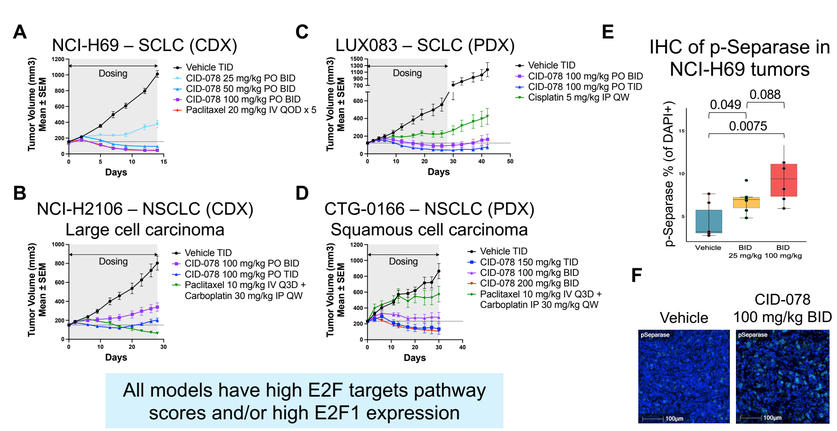


Figure 6. (A) Waterfall plots of sensitivity (GI_{50}), genomic alteration of *TP53* and *RB1*, and heatmaps of E2F targets and G2M checkpoint hallmark pathways Z-scores of 39 breast cancer cell lines tested with CID-078. E2F targets and G2M checkpoint hallmark pathway scores are enriched in TNBC subtype **(B)** Higher E2F targets score and sensitivity to CID-078 is enriched in TNBC. P-values are shown and calculated by Wilcoxon rank sum exact test.

Figure 7. CID-078 shows robust single agent activity and modulation of mitosis specific candidate biomarker p-separase in SCLC and NSCLC CDX/PDX models

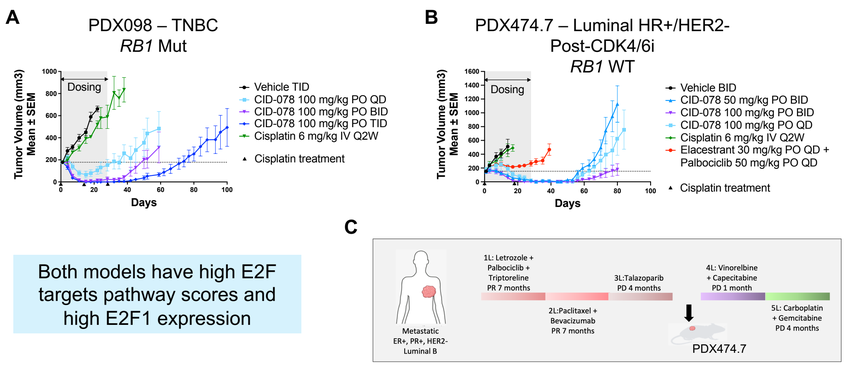


All models have high E2F targets pathway scores and/or high E2F1 expression

Figure 7. *In vivo* SCLC and NSCLC xenograft studies. Mice were inoculated SC with $5x10^6$ NCI-H69 **(A)** or $1x10^7$ NCI-H2106 **(B)** CDX cells, or fragments of LUX083 **(C)** or CTG-0166 **(D)** PDX tumors. Treatment was initiated when tumors reached 100-250 mm^3. CID-078 and controls were administered at the doses indicated. All treatment regimens were tolerated as assessed by body weight measurements (not shown). Efficacy results for NCI-H69 represent two studies where controls behaved consistently. NCI-H69 tumors were collected after six days of treatment and stained for p-separase (S1126). Quantitation of positive cells as a percentage of $DAPI^+$ cells **(E)** and representative images **(F)** are shown.

SC, subcutaneous; PO, orally; BID, twice daily; TID, three times daily; QOD, once every two days; Q3D, once every three days; QW, once weekly; SEM, standard error of mean

Figure 8. CID-078 shows robust single agent activity in a TNBC *RB1* mutant PDX model and a luminal HR+/HER2- post-CDK4/6 inhibitor BC PDX model



Both models have high E2F targets pathway scores and high E2F1 expression

Figure 8. *In vivo* breast cancer xenograft studies. Mice were inoculated SC with fragments of PDX098 **(A)** or PDX474.7 **(B)** PDX tumors. Treatment was initiated when tumors reached 100-300 mm^3. CID-078 and controls were administered at the doses indicated. All treatment regimens were tolerated as assessed by body weight measurements (not shown). Patient clinical history for PDX474.7 is shown **(C)**.

SC, subcutaneous; PO, orally; QD, once daily; BID, twice daily; TID, three times daily; Q2W, once every two weeks; SEM, standard error of mean; PR, partial response; PD, progressive disease

Figure 9. CID-078 shows single agent activity in CDK-RB-E2F dysregulated tumors

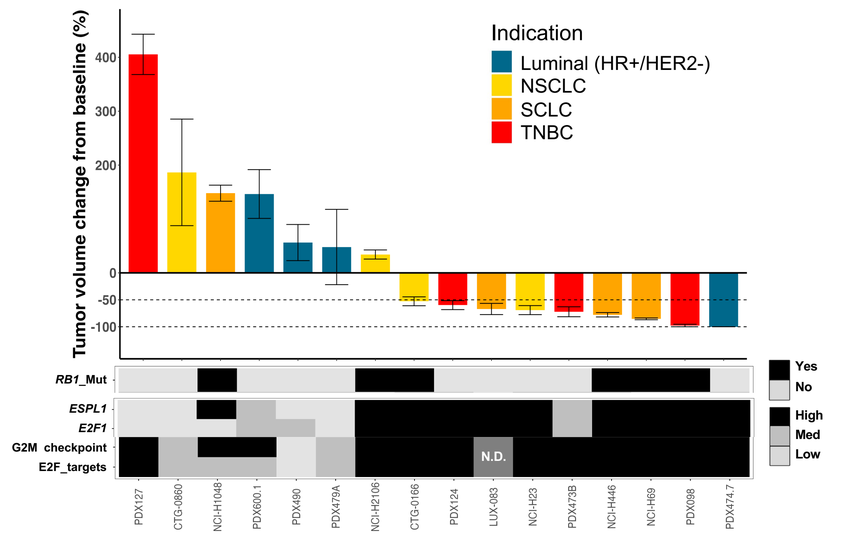


Figure 9. Waterfall plot of *in vivo* efficacy data. Best responses from SCLC, NSCLC, and breast CDX and PDX models is shown along with *RB1* genomic alteration status, *ESPL1* (separase) and *E2F1* gene expression, and G2M checkpoint and E2F hallmark pathway scores. Results for PDX127, PDX124, PDX473B, PDX098, and PDX474.7 are with 100 mg/kg BID dosing of CID-078. Results for CTG-0860, NCI-H1048, PDX600.1, PDX490, PDX479A, NCI-H2106, LUX083, NCI-H23, NCI-H446, and NCI-H69 are with 100 mg/kg TID dosing of CID-078. Results for CTG-0166 are with 200 mg/kg BID dosing of CID-078. N.D., no data.

Figure 10. Now enrolling - CID-AB1-24001 (NCT06577987)

- Phase 1 dose escalation followed by dose expansion
- BOIN-BF design
- Oral dosing
- Pilot food-effect study included
- Primary endpoints: safety, tolerability, PK
- Primary outcome: recommended dose(s) for expansion
- First cohort enrolled
- Currently open sites: START Midwest, START Mountain, NEXT San Antonio
- **Key Inclusion Criteria**
  - Adults with locally advanced or metastatic solid malignancy
  - RECIST v1.1 measurable disease (for patients with NSCLC, SCLC and patients with BC in backfill cohort) or evaluable disease
  - Able to swallow capsules and comply with study requirements
- **Key Exclusion Criteria**
  - Unresolved ≥Grade 2 toxicity from previous tx, except chronic/stable toxicities
  - Brain metastases or spinal cord compression, unless treated and stable
  - Malabsorption or conditions that may interfere with absorption of product

Conclusions

- The pre-clinical data for CID-078 provide compelling proof of concept for CID-078's potential as a novel and differentiated treatment for E2F-driven cancers.
- These data, along with suitable physical and pharmacokinetic properties and established nonclinical safety margins, supported progression of CID-078 into clinical studies.
- A multi-center phase 1 clinical trial (NCT06577987) is currently enrolling patients.