Discovery of CID-078, a first-in-class oral macrocycle cyclin A/B-RxL inhibitor, for the treatment of cancers with Rb-deficiency or hyperactivated E2F

AACR 2026, New Drugs on the Horizon

Marie Evangelista, SVP Head of Research, Circle Pharma

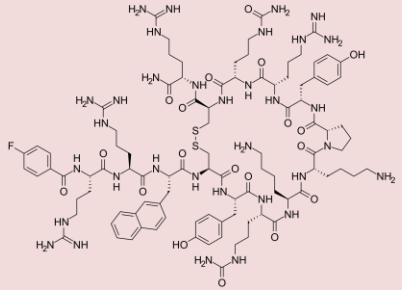
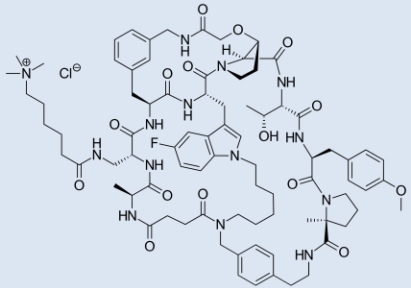
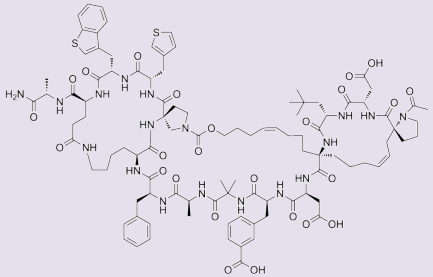
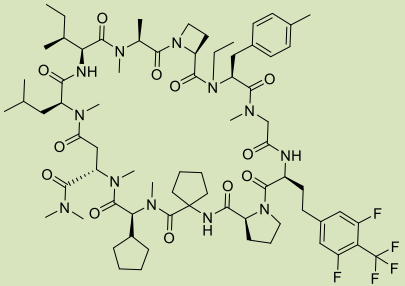
CIRCLE PHARMA

Disclosure slide

I am a Circle Pharma employee

Macrocycles can drug the most challenging targets, including protein–protein interactions (PPIs), but achieving intracellular and oral delivery remains a key unmet challenge in drug discovery

Route of administration

Target	Injectable	Oral
Extracellular	 Motixafortide (CXCR4 inh)	 Enlicitide (PCSK9 inh)
Intracellular	 Zolucatetide (β-catenin/TCF4 inh)	 Paluratide (panRAS inh)

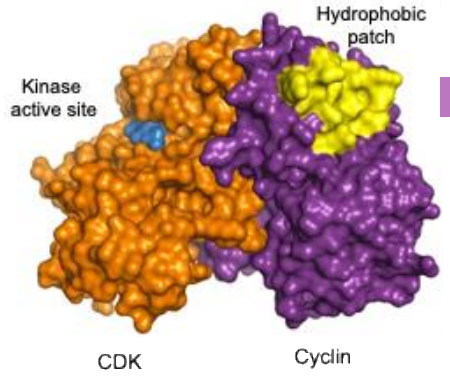
State of the field

- Many peptide therapeutics have neither intrinsic **oral bioavailability** nor **passive cell-membrane permeability**.
- Compounds that **cross cell-membranes** but are not absorbed in the gut require injection.
- Compounds targeting extracellular proteins can be **administered orally** with the help of enabling formulations.
- **Oral delivery** against **intracellular targets** is rare, especially against **novel mechanisms**.

Circle's platform unlocks previously undruggable cyclins with cell-permeable, oral macrocycles

Small molecule CDK inhibitors

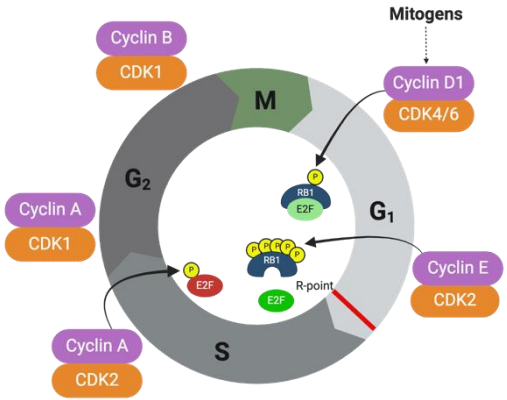
CDK4/6 inh	Approved
CDK2 inh	Phase 1/2
CDK4 inh	Phase 3



Macrocycle cyclin RxL inhibitors

Cyclin A/B	Phase 1
Cyclin D1	IND 2026
other cyclins	Discovery

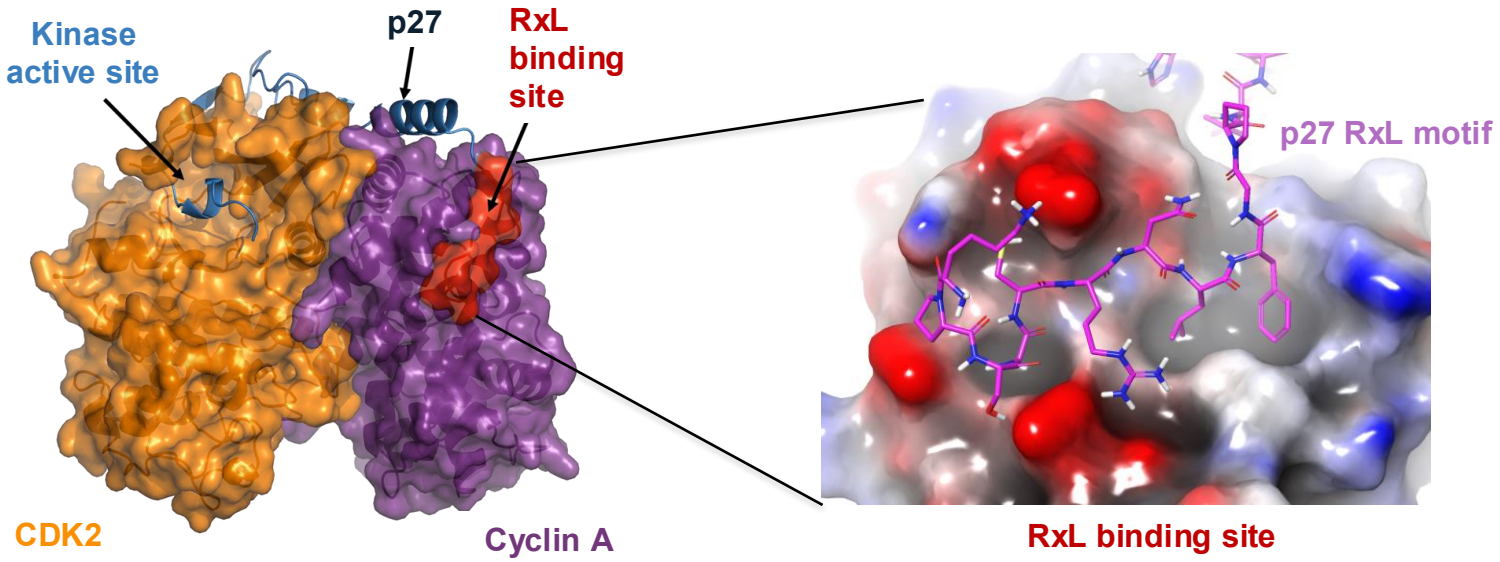
- Cytostatic
- Selectivity and safety
- Resistance
- Competitive



- Undruggable with conventional small molecules
- Differentiated mechanism of action
- Exquisitely selective → compelling safety profile

Substrate recognition by cyclins as an oncology target

Key regulators of the cell cycle, but traditionally considered undruggable



Nobel Laureate **Bill Kaelin** was the first to demonstrate the therapeutic potential of a synthetic lethality mechanism targeting cyclins with RxL peptides.

Chen et al.; *PNAS* **1999** doi: 10.1073/pnas.96.8.4325

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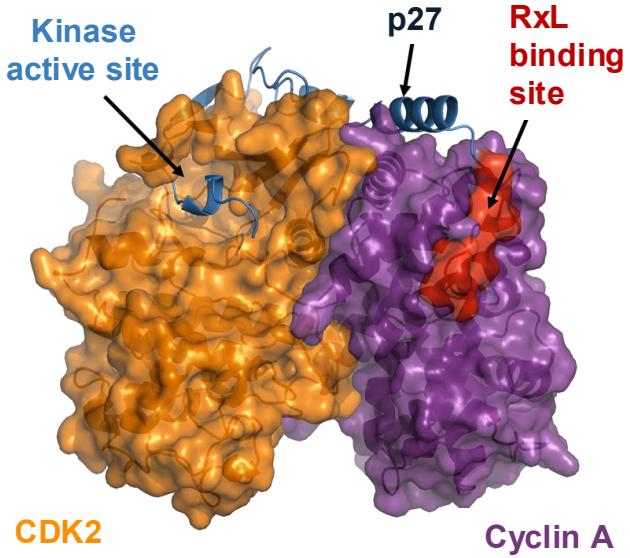
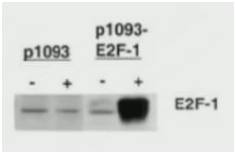
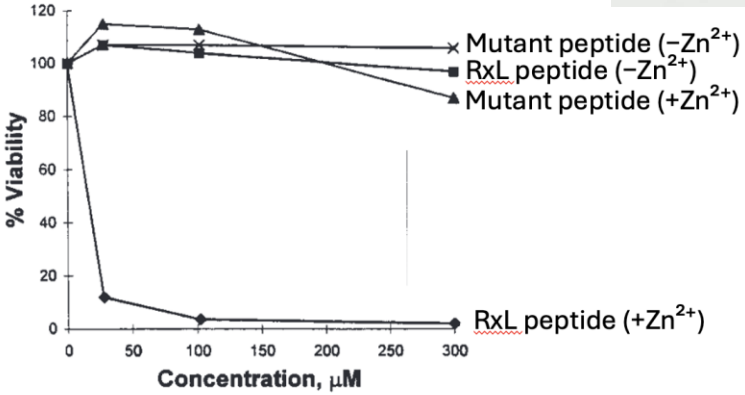


Rat fibroblasts overexpressing E2F1





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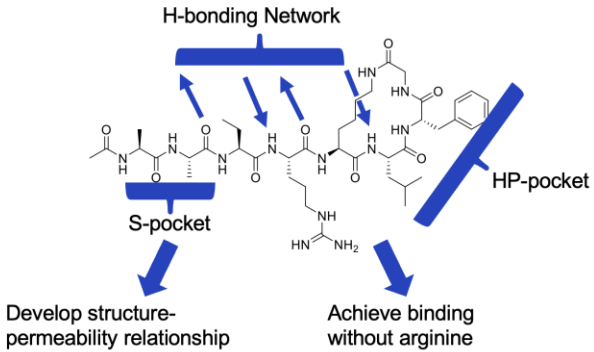
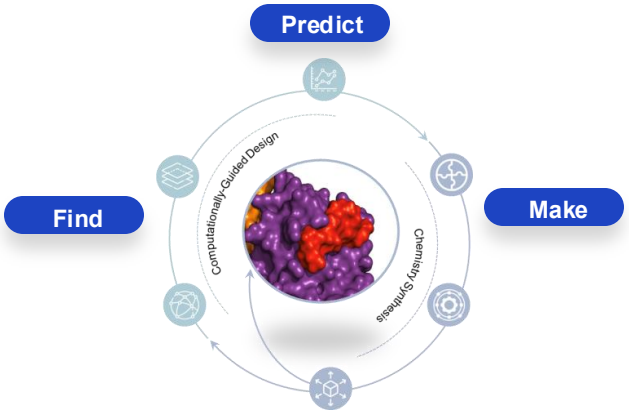
Chen et al.; *PNAS* **1999** doi: 10.1073/pnas.96.8.4325

Strategy for generating potent, permeable, and oral cyclin A RxL macrocycle inhibitors

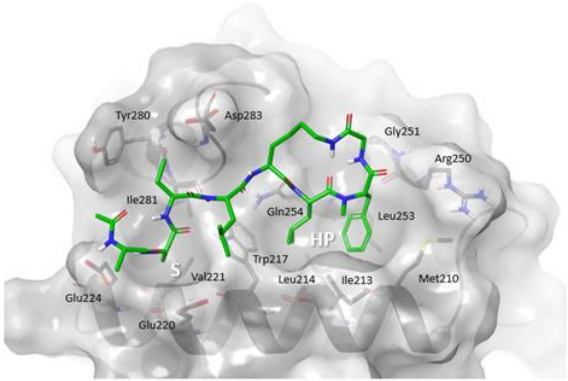
p27 starting point



MXMO™ AI/ML platform



Cyclin A/p27 model



p27 bound cyclin A/CDK2 (PDB: 1JSU). Russo et al.; *Nature* 1996
McInnes et al.; *Curr. Med. Chem.* 2003
Andrews et al.; *Org. Biomol. Chem.* 2004

Improving potency while achieving permeability and oral bioavailability to enable the discovery of CID-078

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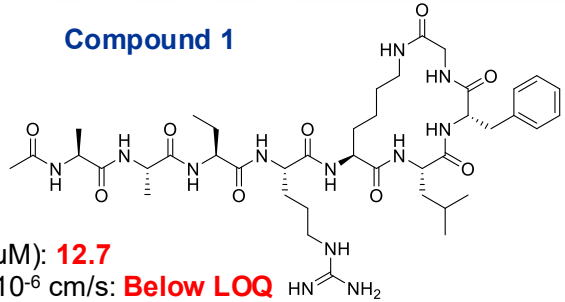
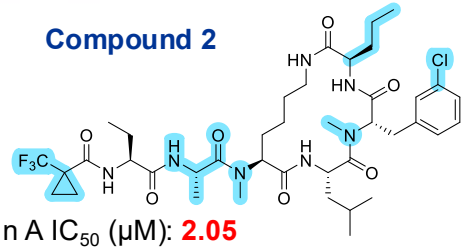
Compound 1



Cyclin A IC_{50} (μM): **12.7**
MDCK Papp x10^{-6} cm/s: **Below LOQ**

Removal of arginine, improve potency and passive permeability

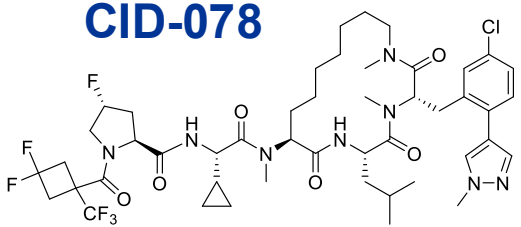
Compound 2



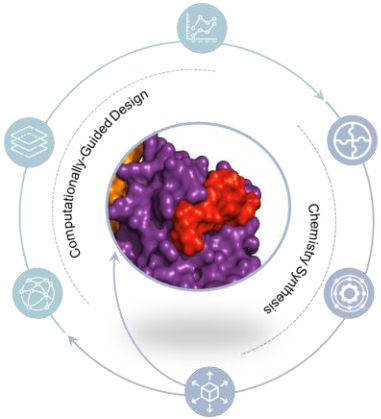
Cyclin A IC_{50} (μM): **2.05**
Cyclin B IC_{50} (μM): **0.047**
MDCK Papp x10^{-6} cm/s: **0.5**
H1048 GI_{50} (μM): **6.85**

Focus on ends of molecule for potency, permeability, cell activity

CID-078

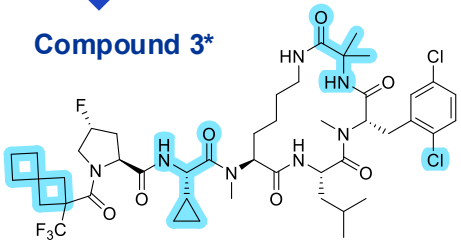


Cyclin A IC_{50} (μM): **< 0.02**
Cyclin B IC_{50} (μM): **< 0.02**
MDCK Papp x10^{-6} cm/s: **6.5**
H1048 GI_{50} (μM): **0.003**
Mouse %F =**25**



Optimize potency and properties**

Compound 3*



Cyclin A IC_{50} (μM): **0.079**
Cyclin B IC_{50} (μM): **< 0.02**
MDCK Papp x10^{-6} cm/s: **3.6**
H1048 GI_{50} (μM): **0.042**
Mouse %F= **2**

*Compound 34 in Bockus et al., *J.Med.Chem.* **2025**
Related efforts in Shapiro et al., *J.Med.Chem.* **2026

Subtle differences in contact points drive cyclin selectivity

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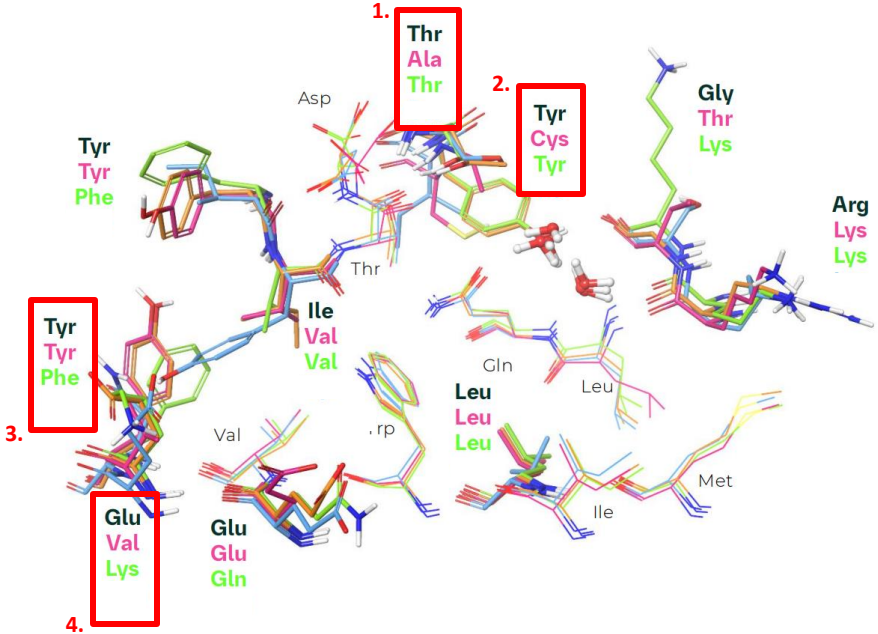
Structural overlay of CID-078-cyclin complexes



Protein	FP Assay [IC_{50} µM]	SPR Affinity [K_D nM]
Cyclin A2	< 0.02	1.1 ± 0.16
Cyclin E1	0.41 ± 0.073	62 ± 19
Cyclin B1	< 0.02	0.83 ± 0.17

CID-078 cyclin A/B RxL Inhibitor: Drug-like properties supporting clinical development

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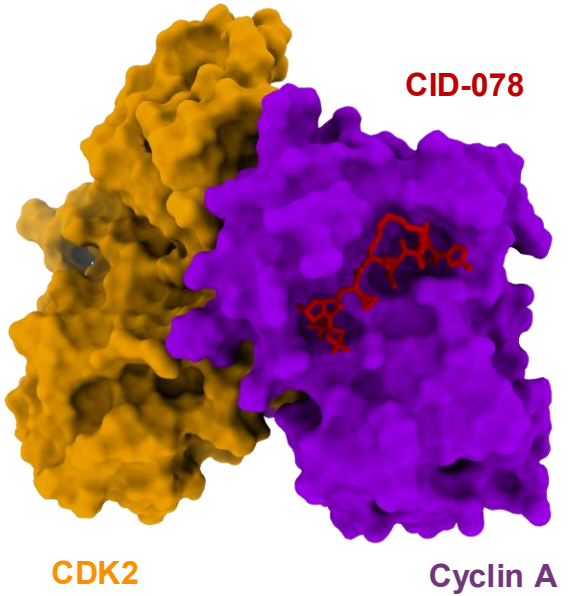
Phys-chem / ADME:
- MW 986; logD = 4.0 with low but workable solubility
- Moderate permeability; P-gp substrate
- Reasonable fu (0.1-0.06) across species
- Stable in plasma & physiological matrices.

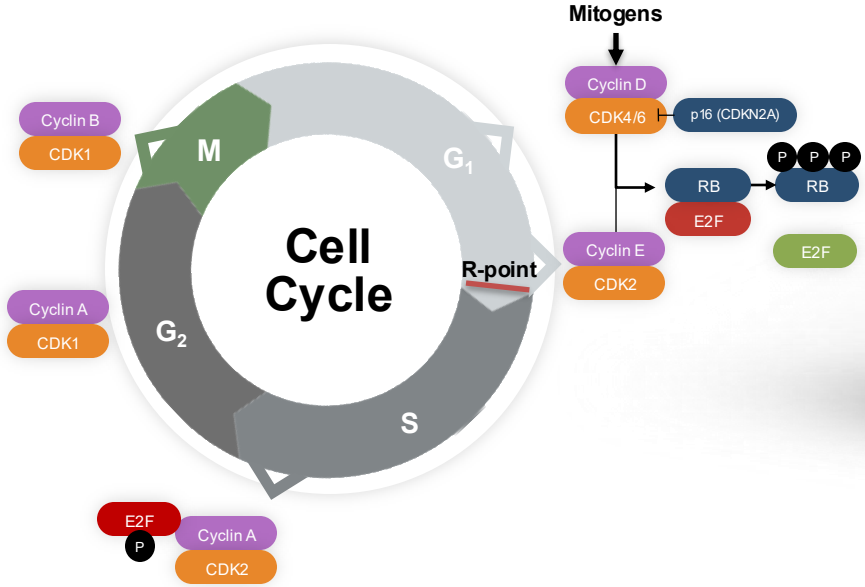
Metabolism / DDI:
- Cross-species metabolism aligned; No human specific metabolites
- Primarily CYP3A4 clearance; low renal, minor biliary
- Moderate in-vitro CYP3A4 inhibition observed

Preclinical PK:
- Moderate–high clearance (rat/dog); predicted human t½, ~3–4 h
- Consistent oral F > 15% across preclinical species (M/R/D/mini-pig)
- Oral F prediction human ~19%



CID-078: Mechanism of action studies

Without drug



Tool A/B inhibitor

nature

Article

Targeting G1–S-checkpoint-compromised cancers with cyclin A/B RxL inhibitors

Pablo Garcia, Catie Gleason
Matt Oser (DCFI)
Deepak Nijhawan (UTSW)
John Doench (Broad, MIT/Harvard)
Benedikt Kessler (Oxford)

Elucidation of the CID-078 mechanism of action using cyclin A/B RxL inhibitor tool compounds (Singh S et al, Nature 2025)

CID-078: Mechanism of action studies

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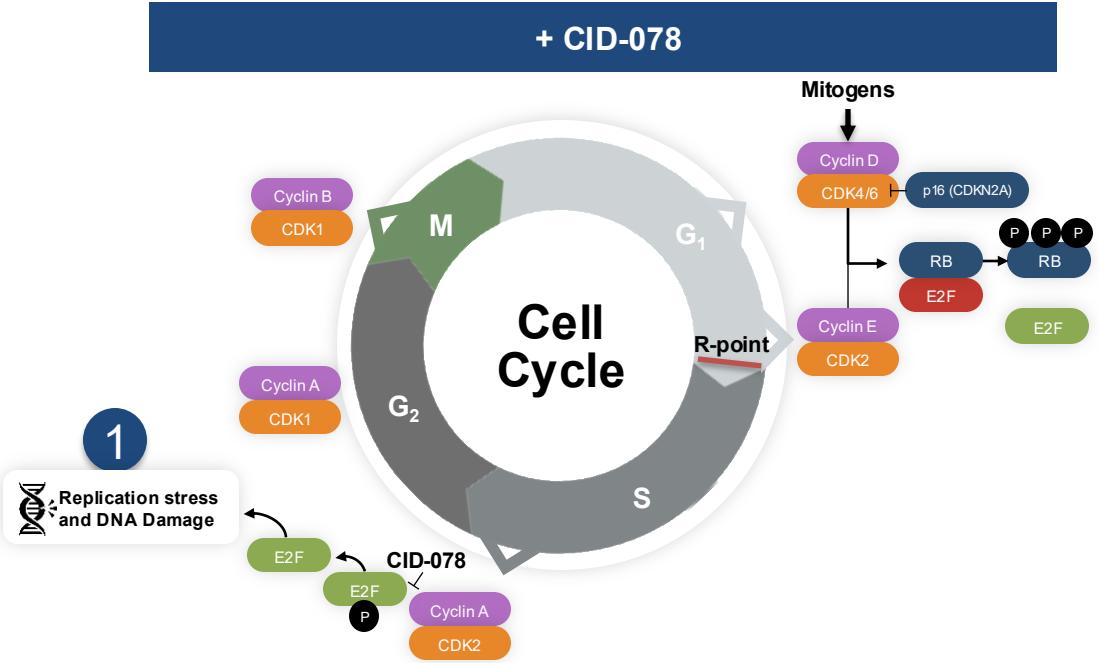

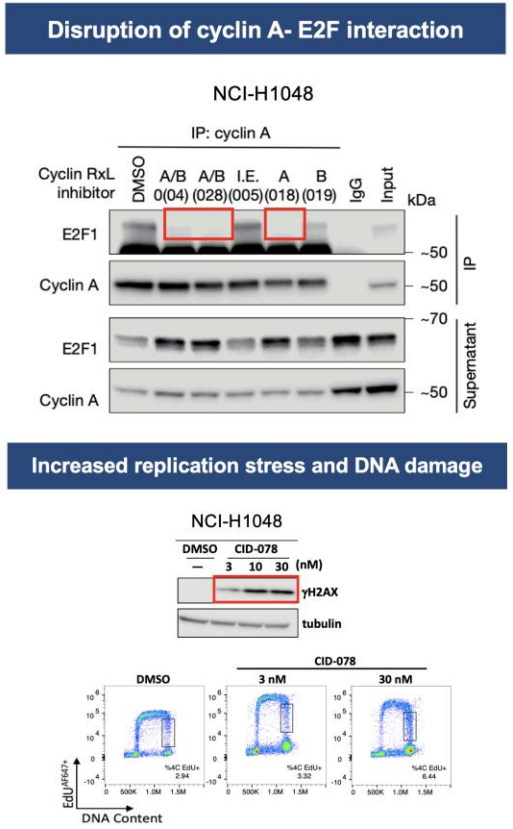

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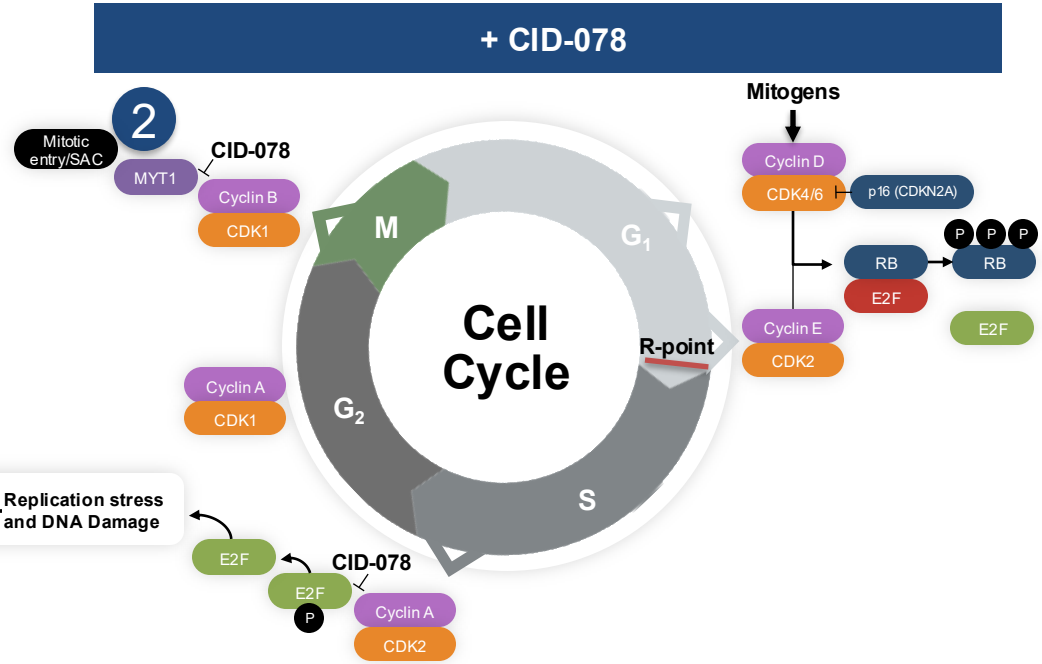
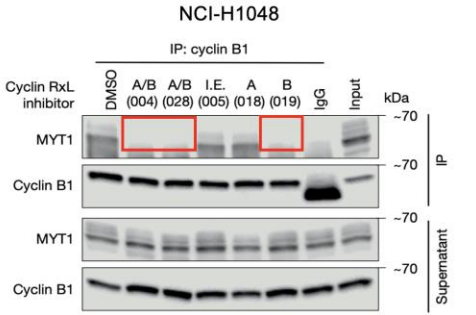
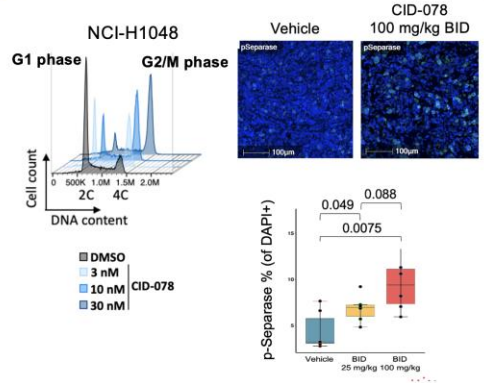
CID-078: Mechanism of action studies



Disruption of cyclin B: Myt1 interaction



Pre-mature mitosis and increased p-Separase

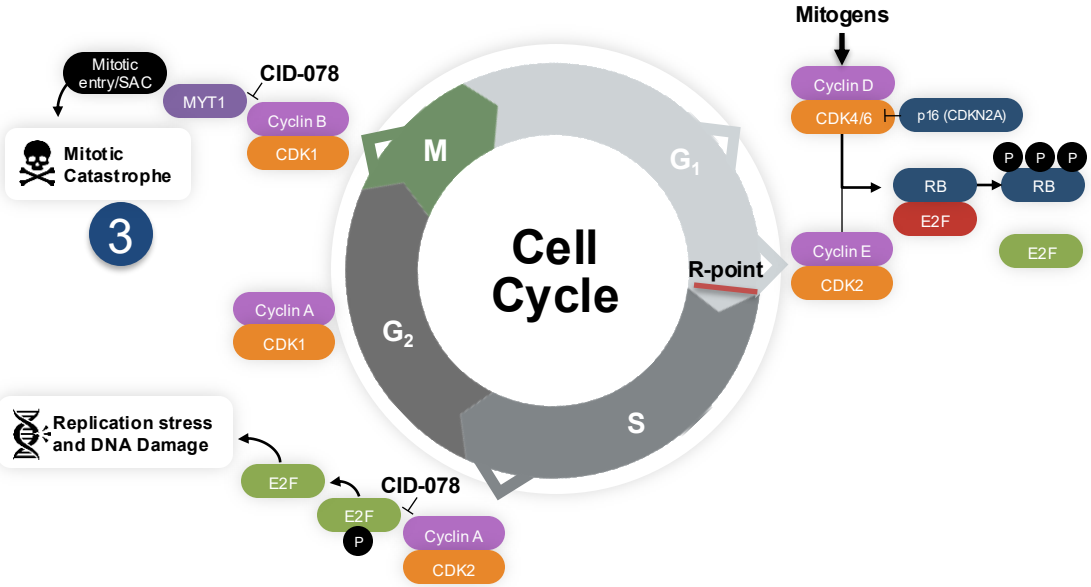


p-Separase as a marker of mitotic progression

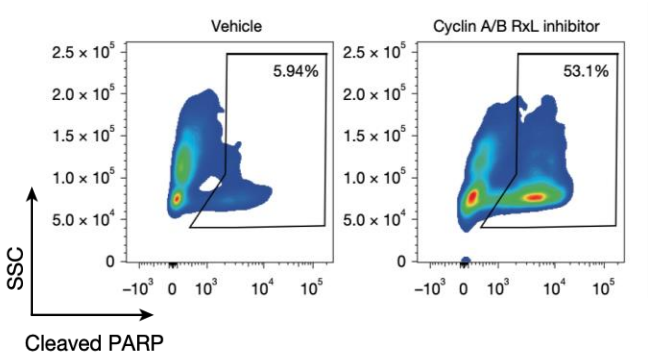
Elucidation of the CID-078 mechanism of action using cyclin A/B RxL inhibitor tool compounds (Singh S et al, Nature 2025.

CID-078: Mechanism of action studies

+ CID-078



Mitotic catastrophe and apoptosis



Elucidation of the CID-078 mechanism of action using cyclin A/B RxL inhibitor tool compounds (Singh S et al, Nature 2025)

Crossing the E2F activity threshold (“tipping point”) during S-phase induces apoptosis

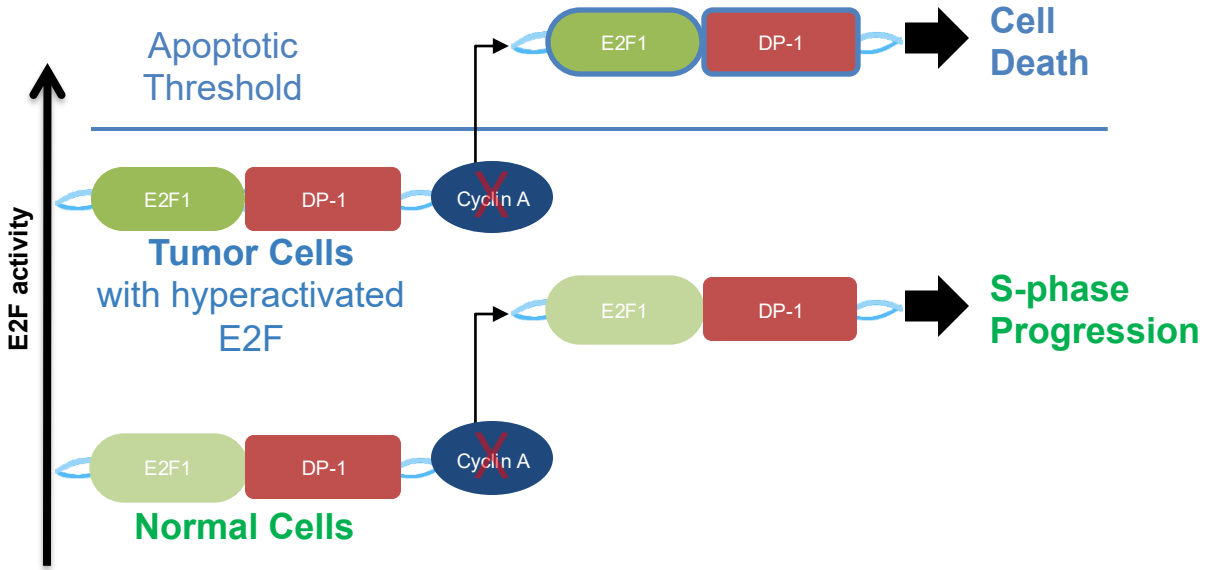
Tumors with hyperactivated E2F susceptible to cell death through cyclin A inhibition

Persistence of E2F during S-phase results in different outcomes based on baseline:

E2F high tumors: Crosses E2F activity threshold (“tipping point”), inducing apoptosis.

Normal cells: Tolerable, and ultimately cells progress through the cycle.

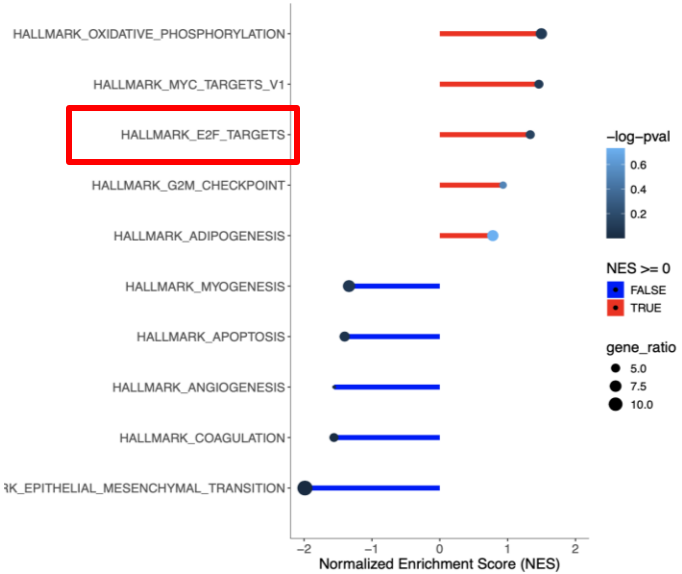
Inhibition of cyclin / CDK during S phase results in persistence of E2F activity



Schematic adapted from Shapiro, Journal of Clinical Oncology (2006)

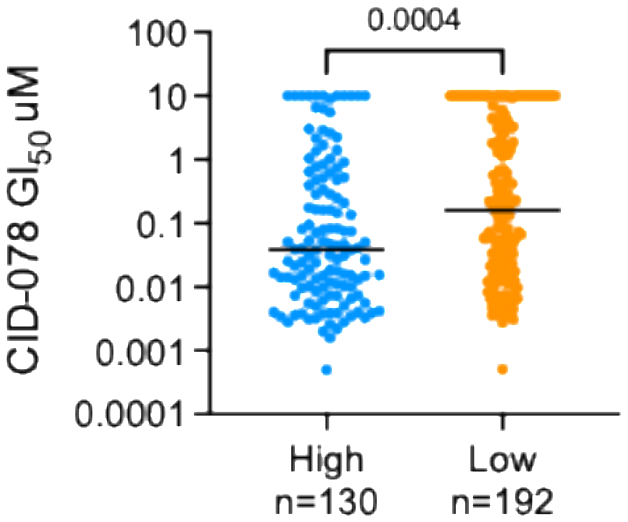
Tumor cell lines that are elevated for E2F activity show increased sensitivity to CID-078

Gene Set Enrichment Analysis (GSEA)



CID-078 sensitivity based on AOC; differential analysis conducted on top 25% sensitive lines vs top 25% resistant lines.

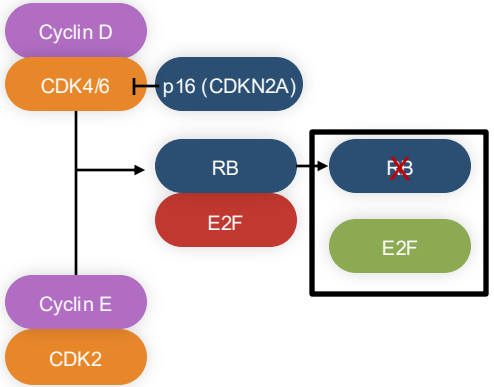
E2F Activity



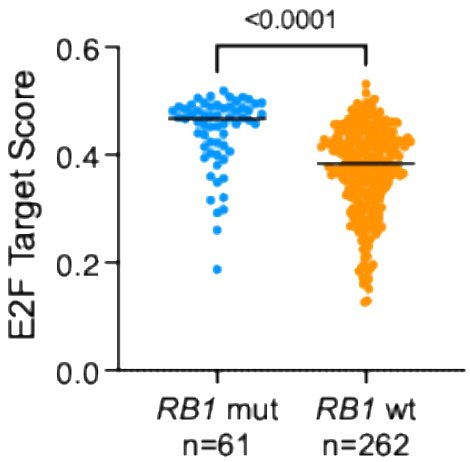
E2F based on E2F Target Hallmark gene set from MSigDB; E2F high vs low defined by median cut-off across cell line panel.

Tumor cell lines that have RB1 alterations show elevated E2F activity

Loss of *RB1* drives hyperactivated E2F



_RB1_ mutation > E2F high



p-values based on Mann-Whitney; *RB1* mutation based on genomic alterations (mutation, indel, deletion); E2F based on E2F Target Hallmark gene set from MSigDB

Tumor cell lines that have RB1 alterations show increased sensitivity to CID-078

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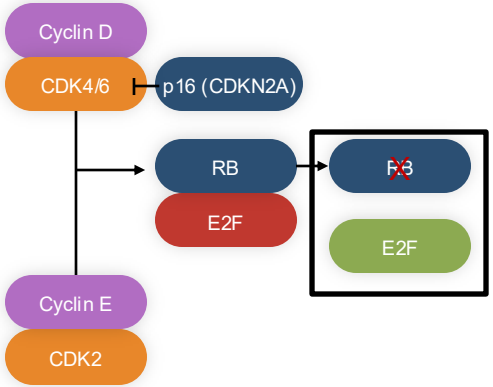
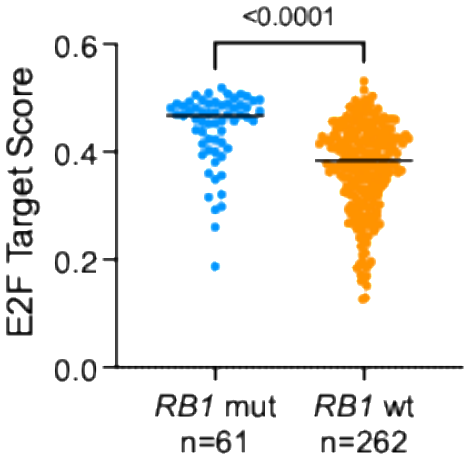
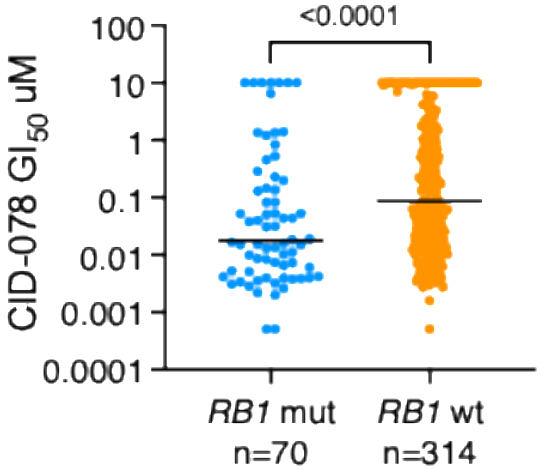


RB1 mutation > E2F high



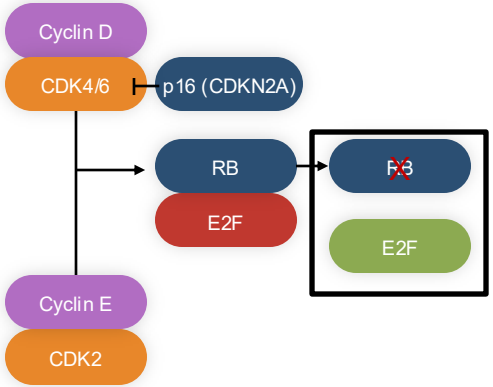
RB1 status > CID-078 sensitivity



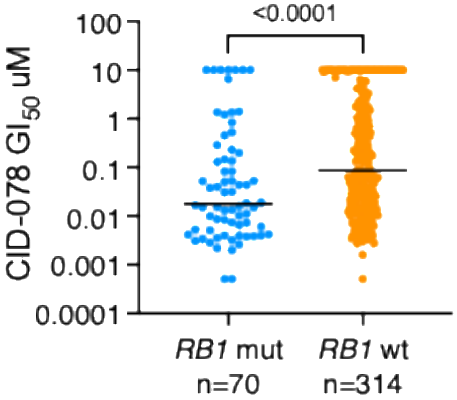
p-values based on Mann-Whitney; *RB1* mutation based on genomic alterations (mutation, indel, deletion); E2F based on E2F Target Hallmark gene set from MSigDB

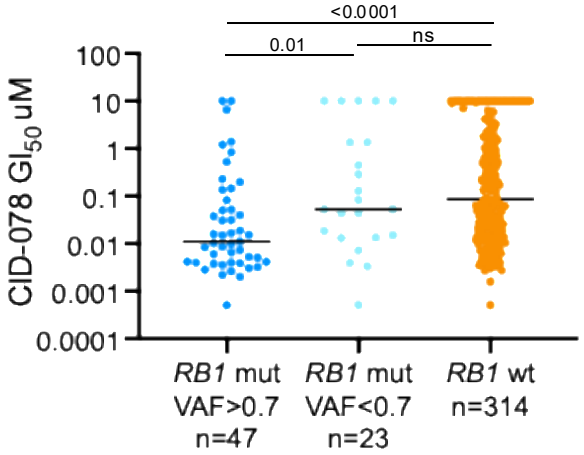
Cell lines with Rb-deficiency or bi-allelic inactivation of *RB1* show enriched sensitivity to CID-078

Loss of *RB1* drives hyperactivated E2F



Cell lines with bi-allelic inactivation of *RB1* are more sensitive to CID-078





p-values based on Mann-Whitney; *RB1* mutation based on genomic alterations (mutation, indel, deletion); E2F based on E2F Target Hallmark gene set from MSigDB

Rb-deficiency: Complete functional loss of Rb, integrating genomic inactivation and protein loss

Rb-deficiency

Next Gen Sequencing

Bi-allelic inactivation (genomic/DNA)

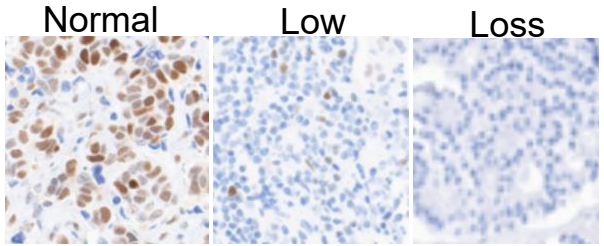
Local NGS test from patient records

RB1 alterations (alt): Sequence or copy number changes (missense, frameshift, truncating, splice-site, or deletion) predicted to impair Rb function

RB1 biallelic inactivation: Complete functional loss of *RB1* due to inactivation of both alleles, via dual alterations or deletion of one allele with alteration of the second

Confirmatory IHC Analysis

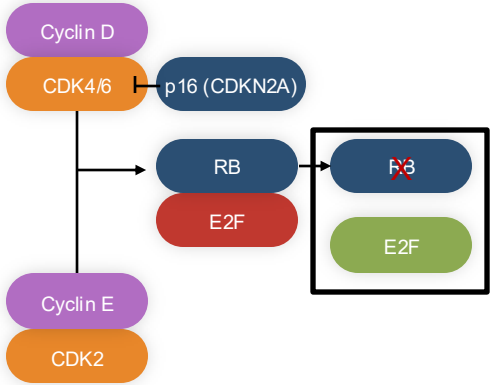
Loss of Rb protein expression



7% of all solid tumors are Rb-deficient

~125,000 new patients in the US per year[1]

Loss of *RB1* drives hyperactivated E2F



Rb-deficient frequency in solid tumors

Tumor type	Rb-deficiency frequency
Breast Cancers	
Basal-like (incl. TNBC)	Up to 70%[2]
HR+ (post CDK4/6i therapy)	Up to 10%[3]
Lung Cancers	
Small cell lung cancer	> 90%[4]
Non-small cell lung cancer	~8%[5]
Neuroendocrine Carcinomas	Up to 70%[6]
Neuroendocrine prostate cancer	Up to 70%[7]
Sarcomas	
Leiomyosarcoma	> 80%[8]
Osteosarcoma	Up to 60%[9]

References: 1. Incidence from ACS Facts and Figures, 2025 2. Mandigo et al., Clin Cancer Res., 2022 3. Andre et al., Annals of Oncology, 2024 4. Febres-Aldana et al., Clin. Cancer Res., 2022 5. Bhateja et al., Cancer Medicine, 2019 6. Venizelos et al., Endocrine-Related Cancer, 2021 7. Beltran et al., Nat Med., 2016 8. Schaefer et al., Cancer, 2021 9. Zoumpoulidou et al., Nature Comms., 2016.

Patient derived Rb-deficient leiomyosarcoma cell lines exhibit increased sensitivity to CID-078

7% of all solid tumors are Rb-deficient

~125,000 new patients in the US per year[1]

Tumor type	Rb-deficiency frequency
Breast Cancers	
Basal-like (incl. TNBC)	Up to 70%[2]
HR+ (post CDK4/6i therapy)	Up to 10%[3]
Lung Cancers	
Small cell lung cancer	> 90%[4]
Non-small cell lung cancer	~8%[5]
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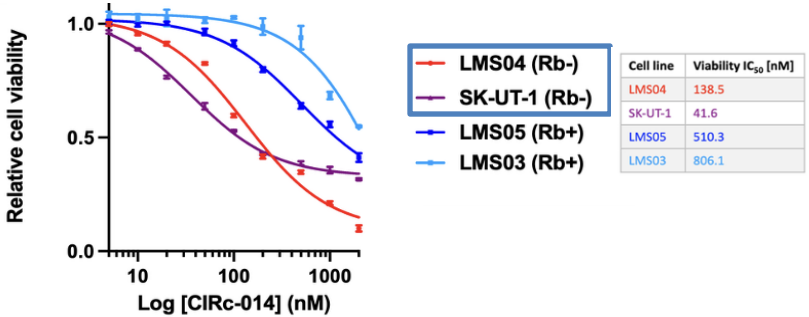
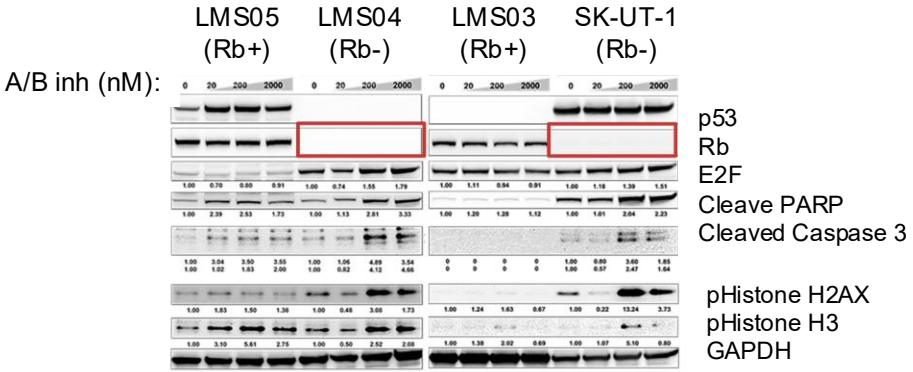
Patient derived leiomyosarcoma cell lines



Cell line	Viability IC_{50} [nM]
LMS04	138.5
SK-UT-1	41.6
LMS05	510.3
LMS03	806.1



Inga-Marie Schaefer, BWH/Harvard Medical School

CID-078 tumor growth inhibition in a SCLC CDX model

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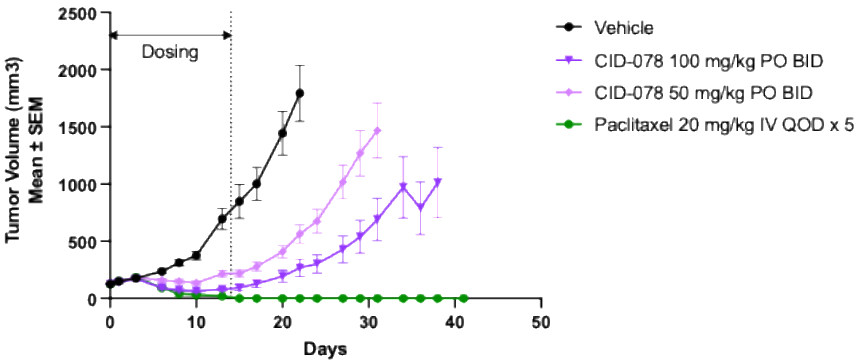
Neuroendocrine prostate cancer	Up to 70%[7]
Sarcomas	
Leiomyosarcoma	> 80%[8]
Osteosarcoma	Up to 60%[9]

NCI-H446 (CDX): *RB1* mut E2F high



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9. Zoumpoulidou et al., Nature Comms., 2016.

CID-078 demonstrates greater activity in an Rb-deficient vs Rb-proficient lung PDX model

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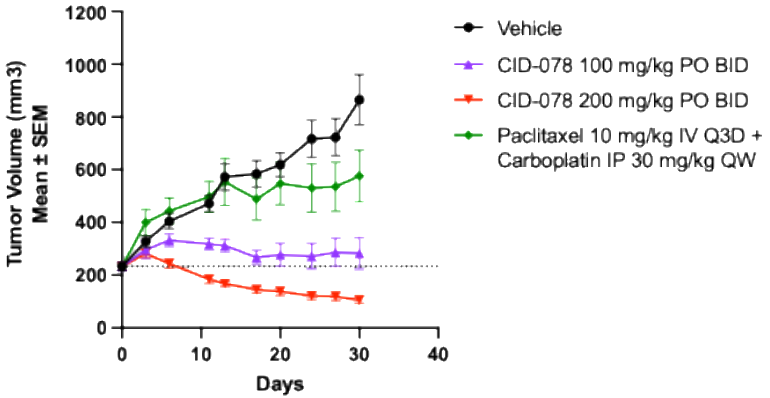
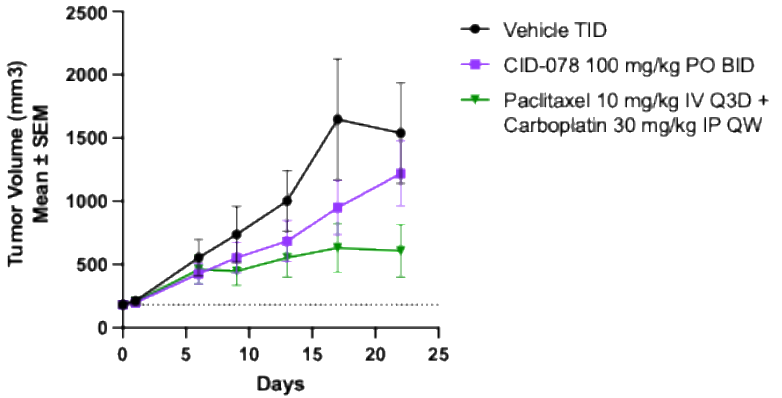
CTG-0166 (PDX): *RB1* mut, E2F high



CTG-0860 (PDX): *RB1* wt, E2F low



CID-078 shows single agent activity in CDK-Rb-E2F dysregulated tumors

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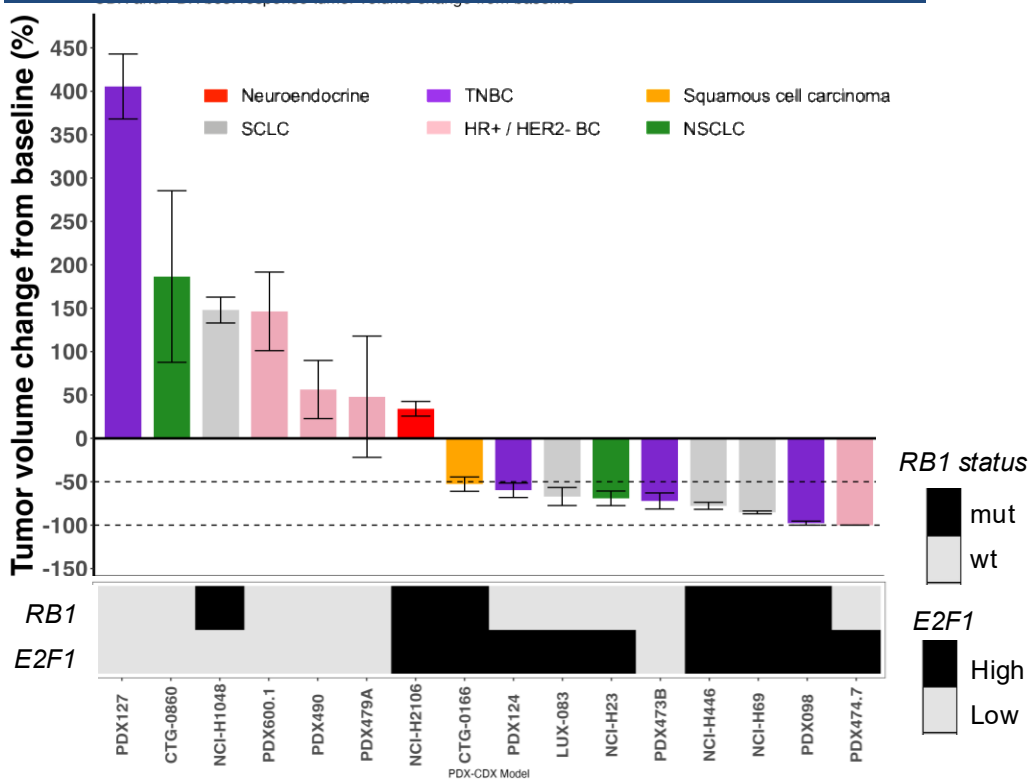
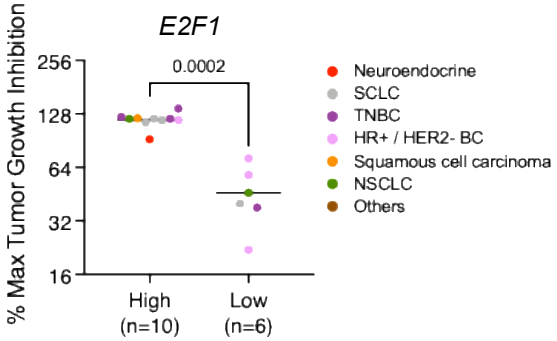
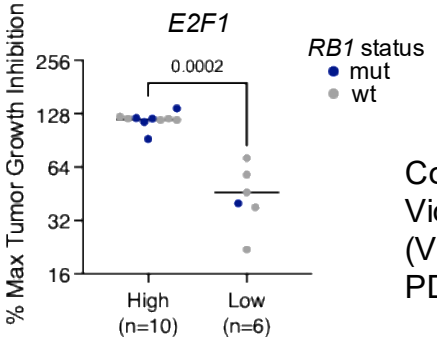
CID-078 efficacy in CDX and PDX models



Indication



RB1 status



Collaboration with Violetta Sera (VHIO) on breast PDX models

CID-078 Summary

- First-in-class: Oral macrocycle targeting a previously undruggable hydrophobic patch on cyclin A/B complexes
- Mechanism: Dual cyclin A/B inhibition drives replication stress and mitotic catastrophe, leading to tumor cell death
- Biomarker hypothesis: Enriched activity in E2F-high or Rb-deficient cancers
- First-in-human Phase 1 trial evaluating CID-078 in solid tumors currently enrolling (NCT06577987)

Acknowledgments

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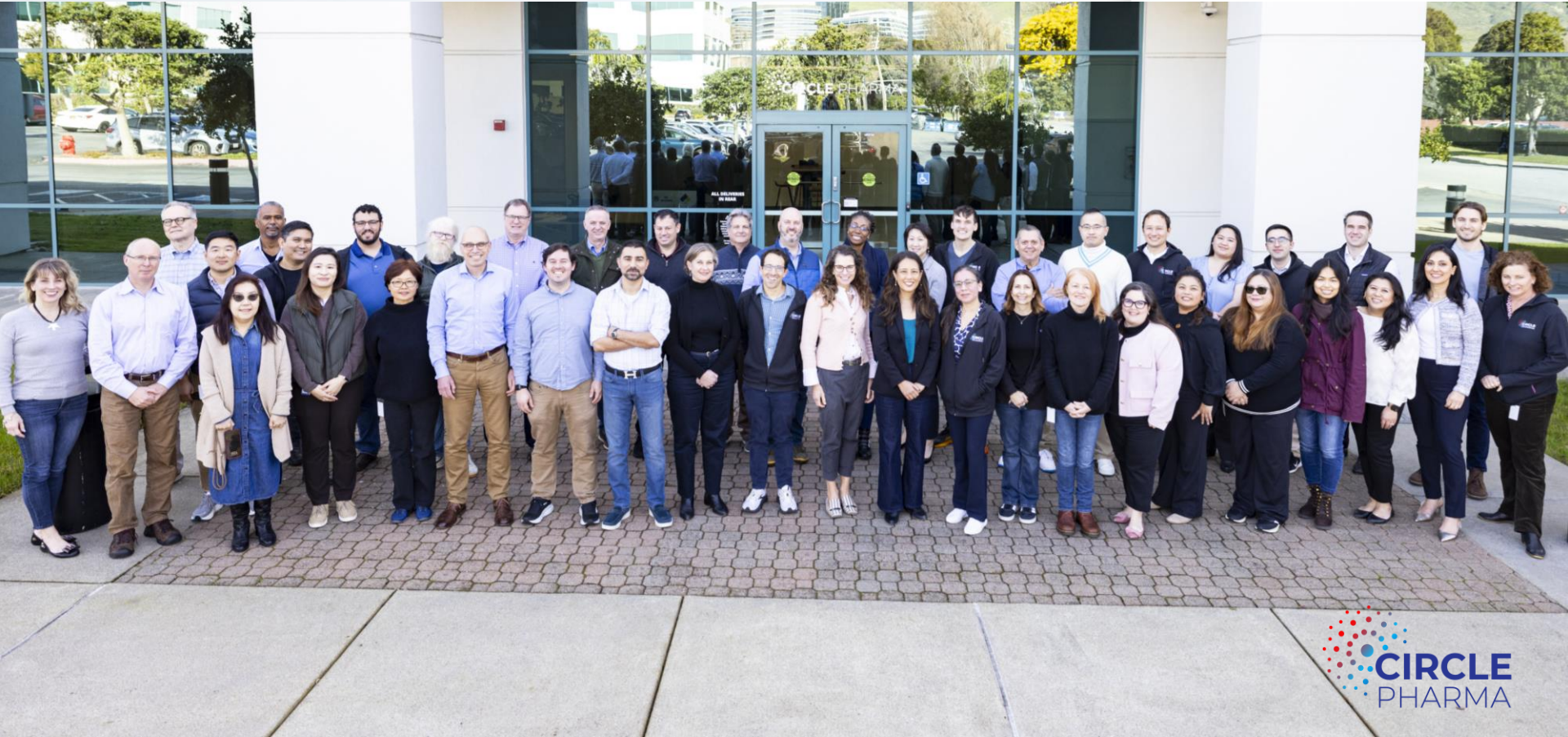

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Nathan Dupper
Breena Fraga-Walton
Andy Bockus
Miguel Baldomero
Luis Hernandez
Joshua Luna
Megan DeMart
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Meisam Nosrati
Daphne He
Gavin Situ
Pablo D. Garcia
Bernard Levin
Li-Fen Liu
Peadar Cremin
Jinshu Fang
Evelyn W. Wang

Collaborators (pre-clinical)

Matt Oser (DCFI)
Shilpa Singh (DCFI)
Yavuz T. Durmaz (DCFI)
Violetta Sera (VHIO)
Cristina Molina (VHIO)
Andreu Odena Bermudo (VHIO)
Marcos Malumbres (VHIO)
Benedikt Kessler (Oxford)
Roman Fischer (Oxford)
John G. Doench (Broad,MIT/Harvard)
Deepak Nijhawan (UTSW)
Inga-Marie Schaefer (BWH/Harvard)
Geoff Shapiro (BWH/VHIO)

Scientific Advisors

William G. Kaelin Jr.
Matthew P. Jacobson
Steve Kelsey
Alan Ashworth
John Josey
Bruce Stillman

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