Orally bioavailable peptide macrocycles disrupting intracellular protein-protein interactions: selective inhibitors of the RxL binding site of cyclin family proteins

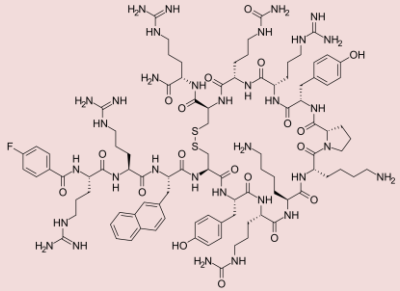
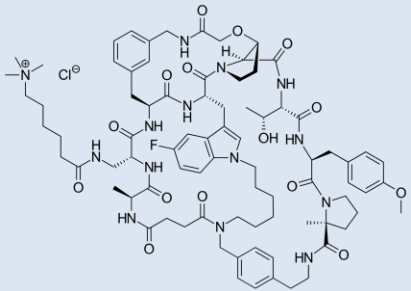
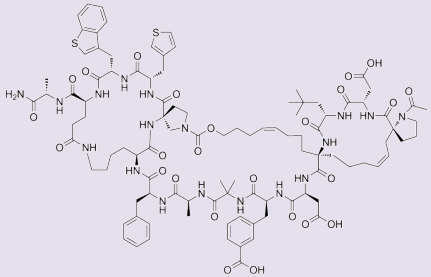
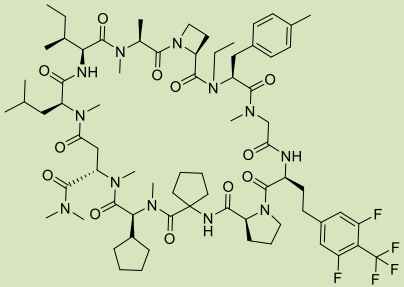
ACS Spring 2026, New Frontier: Enabling Novel Molecular Entities as Drugs
Justin Shapiro, Sr. Scientist, Circle Pharma

CIRCLE PHARMA

Challenging limits in peptide drug discovery

AACR American Association for Cancer Research
Annual Meeting
April 17-22, 2026 SAN DIEGO
AACR.ORG/AACR2026 | #AACR26

Route of administration

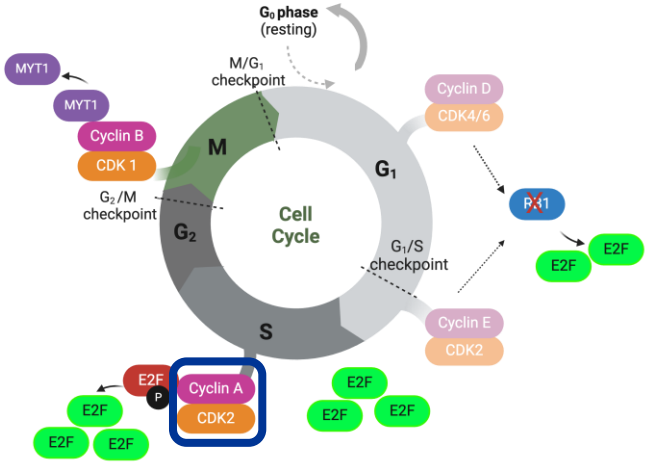
Target	Injectable	Oral
Extracellular	 Motixafortide (CXCR4 inh)	 Enlicitide (PCSK9 inh)
Intracellular	 Zolucatetide (β-catenin/TCF4 inh)	 Paluratide (panRAS inh)

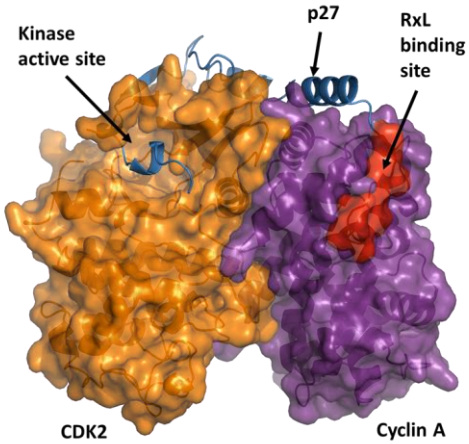
State of the field

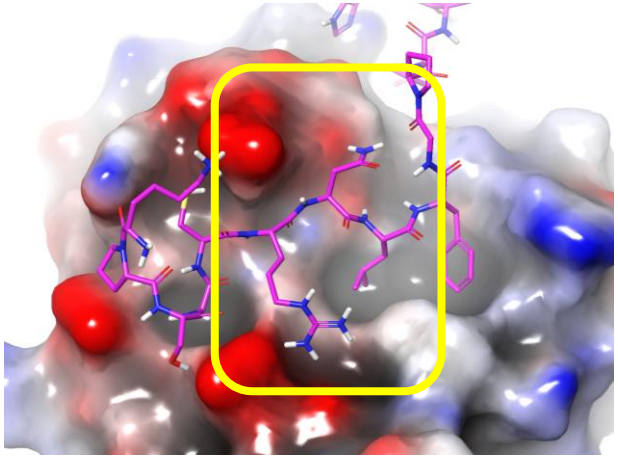
- Many peptide therapeutics have neither intrinsic **oral bioavailability** nor **passive cell-membrane permeability**.
- Compounds that **cross cell-membranes** but are not absorbed in the gut require injection.
- Compounds targeting extracellular proteins can be **administered orally** with the help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

Substrate recognition by cyclins as an oncology target

Key regulators of the cell cycle, but traditionally considered undruggable





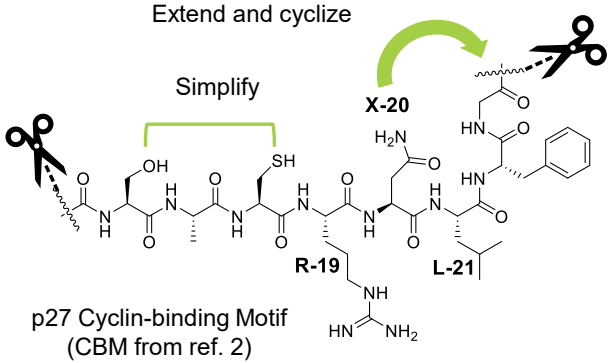


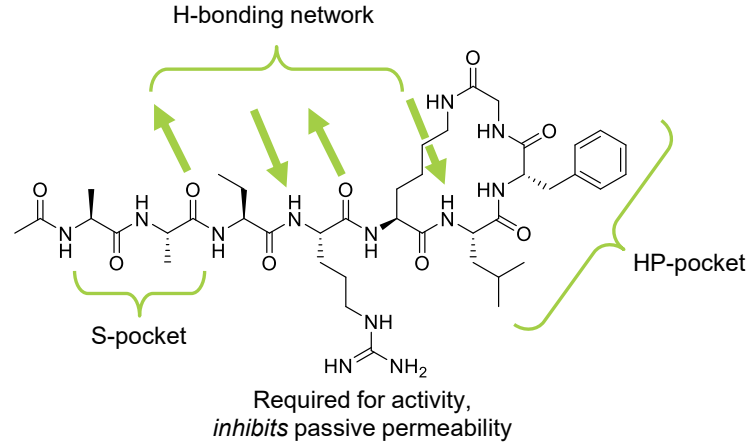
RxL binding site

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

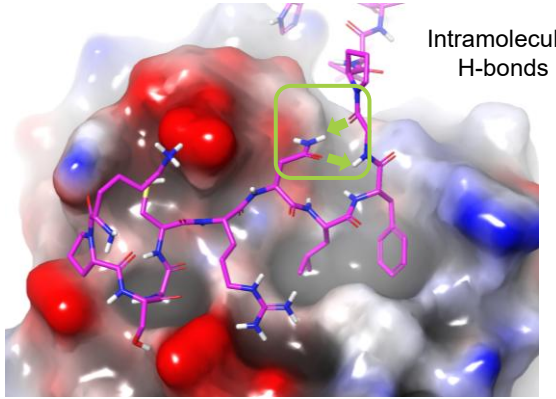
Chen et al.; *PNAS* **1999** doi: 10.1073/pnas.96.8.4325

Previous structure-based drug design led from endogenous binder p27 to an active, but impermeable, macrocycle





Compound 1
(5a from ref. 3)



Cmpd	Cyclin A Binding assay IC_{50} (mM)	CDK2A-Rb Kinase assay IC_{50} (mM)
p27 CBM	3.8	6.1
1	0.63	0.53

Computational modeling

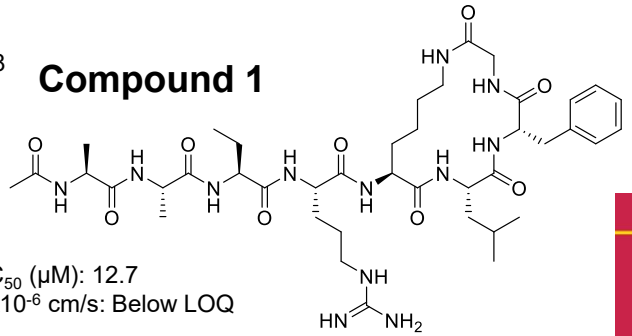
↓

Strategy for binding without Arg

1) p27 bound cyclin A/CDK2 (PDB: 1JSU). Russo et al.; *Nature* **1996**
2) McInnes et al.; *Curr. Med. Chem.* **2003,** doi: 10.2174/1568011033353506
3) Andrews et al.; *Org. Biomol. Chem.* **2004,** doi: 10.1039/b409157d

Development of passively permeable inhibitors

Compound 1



Rot. Bonds: 18

tPSA: 323.8

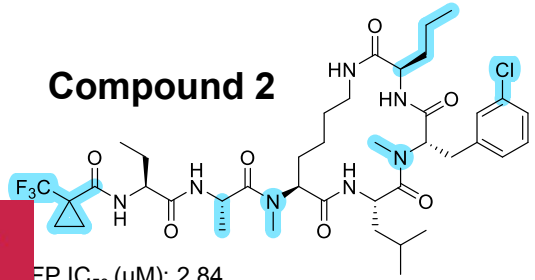
CLogP: -0.18

HBDs: 12

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

Passively permeable +
cell-active hit identification

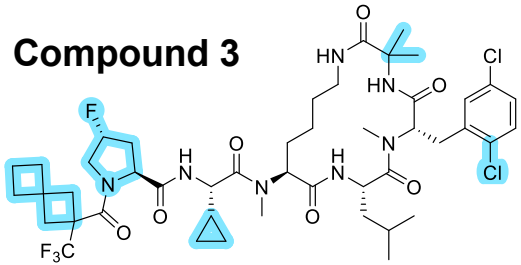
Compound 2



FP IC_{50} (μM): 2.84
I_{50} (μM): 7.72
app x10^{-6} cm/s: 0.5

Hit-to-lead for POC
efficacy by injection

Compound 3



Potency/Selectivity

Cyclin A SPR KD (nM): 9.49

Cyclin B SPR KD (nM): 3.71

Cyclin E SPR KD (nM): 211

NCI-H69 GI_{50} (μM): 0.016

WI-38 GI_{50} (μM): 9.27

Properties

MW: 972.9

tPSA: 177.3

CLogP: 7.48

Rot. Bonds: 10

HBDs: 4

***In Vitro* DMPK**

Caco-2 A-B P_{app}: 0.

Caco-2 B-A P_{app}: 8.

Efflux ratio: 22

Mouse PPB: 96.7%

KSol (μM): 18.9

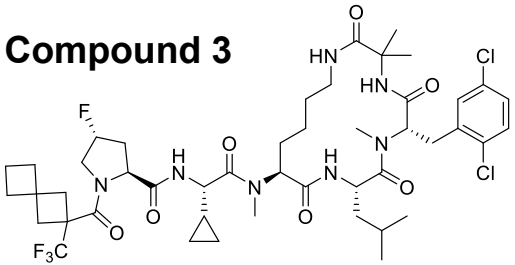
LogD: 5.54

Tumor regression at 100 mpk IP QD
2% oral bioavailability, insufficient for advancement

Bockus et al.; *J. Med. Chem.* **2025** doi: 10.1021/acs.jmedchem.5c00253

Development of an orally bioavailable compound

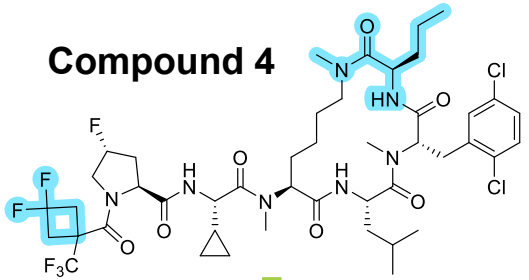
Compound 3



Cyclin A FP IC_{50} (μM): 0.079
H1048 GI_{50} (μM): 0.042
MDCK Papp x10^{-6} cm/s: 3.6

Lariat methylation +
fine-tuning lipophilicity

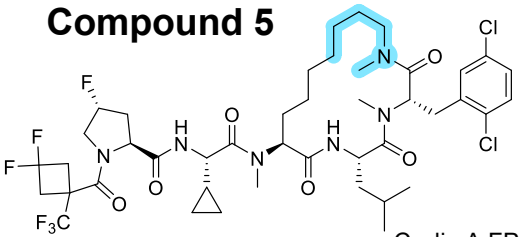
Compound 4



Cyclin A FP IC_{50} (μM): 0.077
H1048 GI_{50} (μM): 0.031
MDCK Papp x10^{-6} cm/s: 5.5

Complete residue
replacement

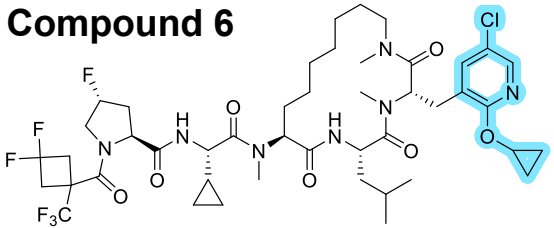
Compound 5



Cyclin A FP IC_{50} (μM): 0.035
H1048 GI_{50} (μM): 0.026
MDCK Papp x10^{-6} cm/s: 9.0
Ksol (μM): 2.8
%PPB: >99

Optimizing PK parameters

Compound 6

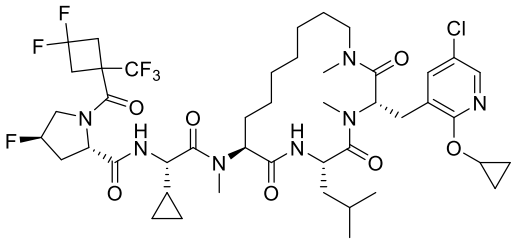


Cyclin A FP IC_{50} (μM): 0.050
H1048 GI_{50} (μM): 0.015
MDCK Papp x10^{-6} cm/s: 13.2
KSol (μM): 27.3
%PPB: 96.6

Shapiro et al.; *J. Med. Chem.* **2026** doi: 10.1021/acs.jmedchem.5c02445
Published as part of Journal of Medicinal Chemistry special issue "Peptide Therapeutics".

Lead compound 6 *in vitro* and *in vivo* profile supports nomination into oral efficacy studies

Compound 6



Biochemical

Cyclin A SPR KD (nM): 2.7

Cyclin B SPR KD (nM): 1.0

Cyclin E SPR KD (nM): 33.8

Cyclin A/B vs E Selectivity: >12

Cellular

NCI-H1048 GI_{50} (uM): 0.015

NCI-H446 GI_{50} (uM): 0.042

NCI-H69 GI_{50} (uM): 0.004

WI-38 GI_{50} (uM): 19.06

Properties

MW: 962.5

tPSA: 161.56 ↓

CLogP: 7.6

Rot. Bonds: 12

HBDs: 2 ↓

In vitro DMPK

KSol (μM): 27.3 ↓

LogD: 3.86

MDCK P_{app}: 13.20

Mouse PPB: 96.6%

Route (Mouse)	Dose (mg/kg)	Tmax (h)	C_{max} Total drug (ng/mL)	C_{max} Free drug (ng/mL)	AUC-inf (ng*h/mL)	$T_{1/2}$ (h)	Cl (mL/min/kg)	%F PO
IV	2	-	-	-	489.86	1.37	68.05	-
PO	30	1.0	1210.00	60.52	2002.23	0.99	-	27.2
PO	100	0.5	2990.00	101.66	8112.69	3.15	-	34.9

- Clean profile in KinomeScan and Eurofins safety/pharmacology panel (GPCRs, ion channels, NHRs, non-kinase enzymes, and transporters).

Shapiro et al.; *J. Med. Chem.* **2026** doi: 10.1021/acs.jmedchem.5c02445
Published as part of Journal of Medicinal Chemistry special issue "Peptide Therapeutics".

Compound 6 demonstrates oral efficacy in cell-line derived xenograft mouse models of small-cell lung cancer

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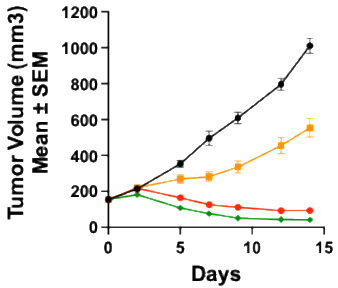
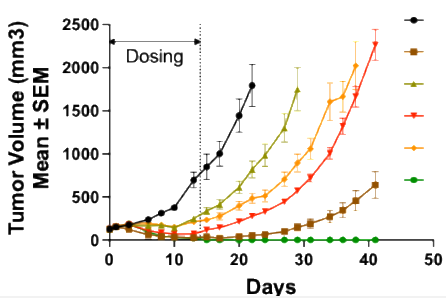
NCI-H69

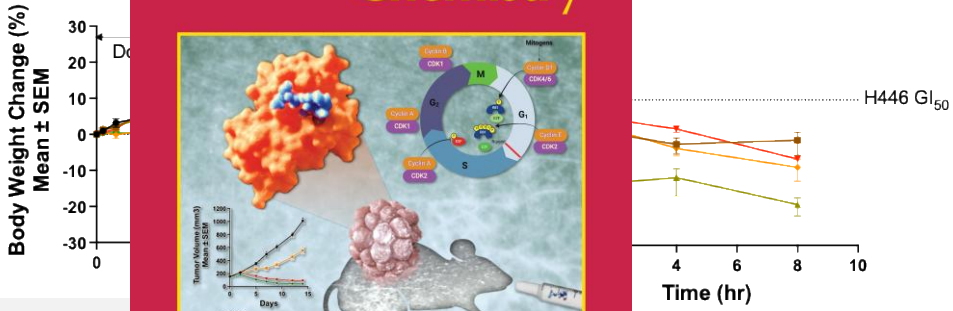


- Vehicle
- Compound **6** 50 mg/kg PO BID
- Compound **6** 25 mg/kg PO BID
- Paclitaxel 20 mpk IV QOD x5

NCI-H446



- Vehicle
- Compound **6** 100 mg/kg PO TID
- Compound **6** 25 mg/kg PO TID
- Compound **6** 100 mg/kg PO BID
- Compound **6** 55 mg/kg PO BID
- Paclitaxel 20 mpk IV QOD x5



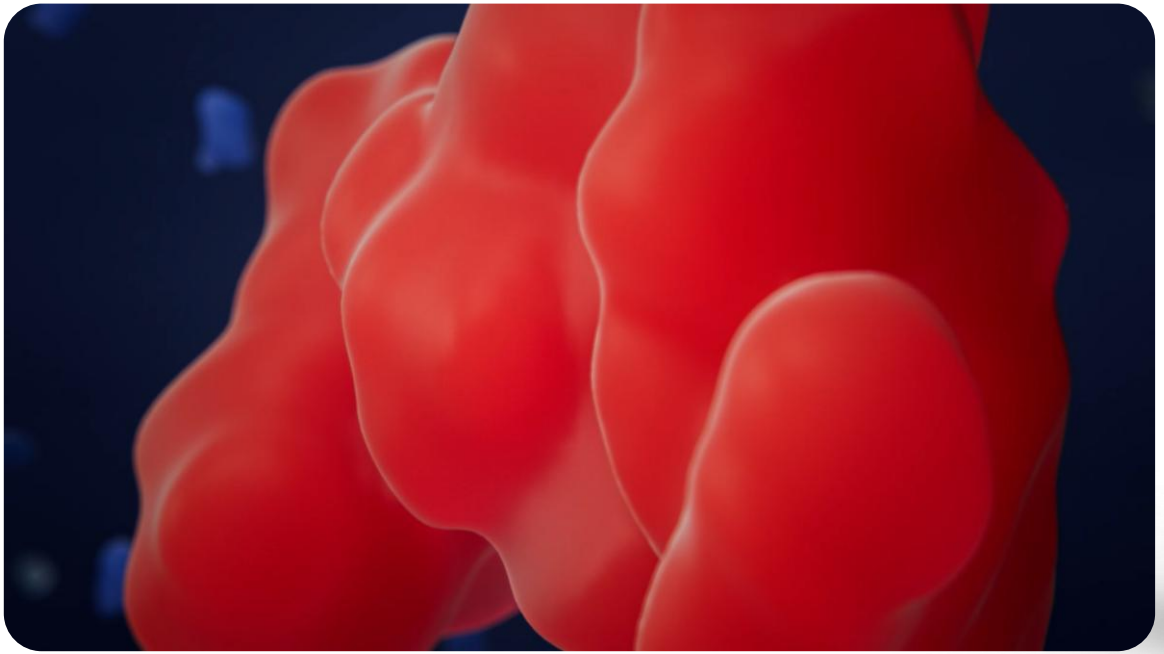
PDX models of triple-negative breast cancer show similar results.

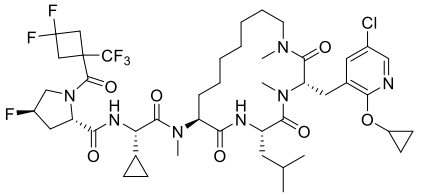
Molina et al.; *AACR-NCI-EORTC* **2023**

Shapiro et al.; *J. Med. Chem.* **2026** doi: 10.1021/acs.jmedchem.5c02445
Published as part of Journal of Medicinal Chemistry special issue "Peptide Therapeutics".

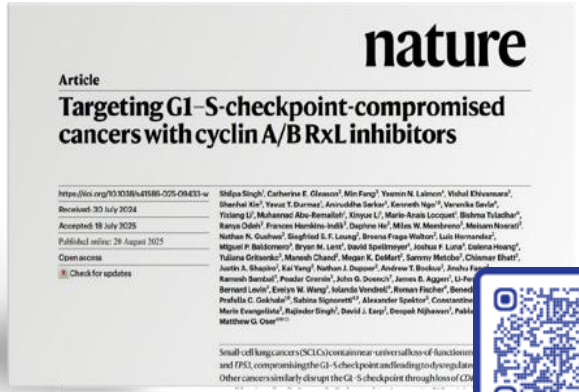
First-in-class oral macrocycle cyclin A/B RxL inhibitors

Selectively cytotoxic in *RB1* altered and E2F-driven tumors





Compound 6 (CIRc-014)
close analog of clinical candidate CID-078



nature

Article

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

CID-078 currently in Ph.1 (NCT06577987).

Singh S. et al.; *Nature*, **2025** doi: 10.1038/s41586-025-09433-w

Circle Pharma's cyclin expertise led to identification of a Cyclin D1 inhibitor – a "holy grail" oncogene target

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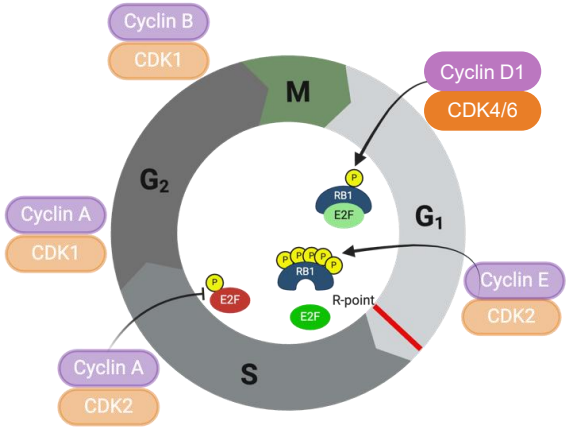


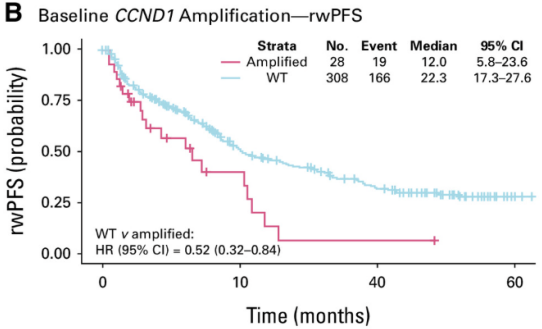
Cyclin D1 Alteration	Indication
Translocation (11;14)	Mantle cell lymphoma
	B-cell lymphoma
	Multiple myeloma
Dependency and/or Amplification	ER+ Breast*
	Head and neck
	Bladder
	Gastric
	Esophageal
	Melanoma
	Neuroblastoma

*Lineage context, not copy number alone, predicts D1 dependency in ER+ breast cancer.

Circulating Tumor DNA Genotyping of Intrinsic and Acquired Gene Alterations in Patients With Advanced Breast Cancer Receiving Palbociclib: Biomarker Results From POLARIS Study

Authors: Debu Tripathy, MD, Joanne L. Blum, MD, PhD, Hong Zhang, PhD, Shibing Deng, PhD, Steven L. McCune, MD, PhD, Kamal Patel, MD, MS, Yao Wang, MD, ... SHOW ALL ..., and Aditya Bardia, MD | AUTHORS INFO & AFFILIATIONS

Publication: JCO Precision Oncology • Volume 9 • https://doi.org/10.1200/PO-24-00810



Progression-free survival on Palbociclib is worse in patients with cyclin D1 amp.

First-in-class isoform selective cyclin D1 RxL inhibitor, IND filing expected by year-end 2026.

The Cancer Genome Atlas (2018), Lakshman A (2018), Diamantidis (2022), Sicinski and Weinberg, Cell 1995

Rationale for targeting cyclin D1:

Achieving “CDK4/6-like” efficacy while reducing hematologic adverse events

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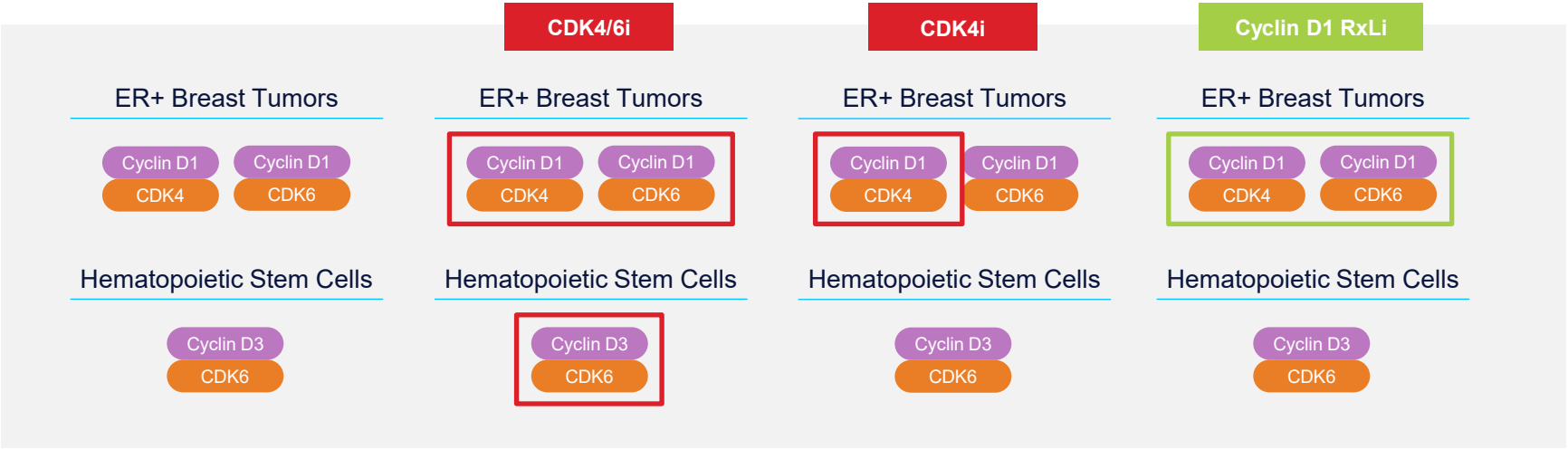
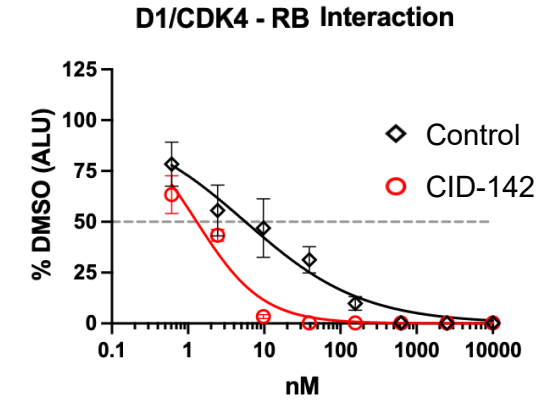
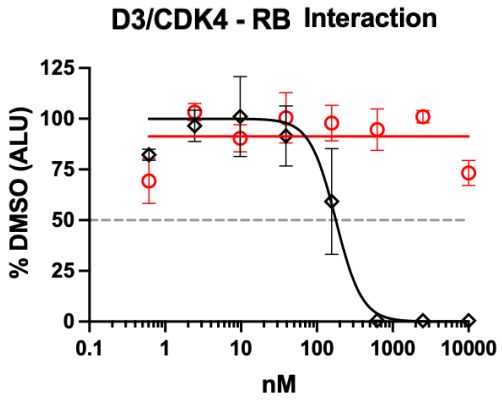


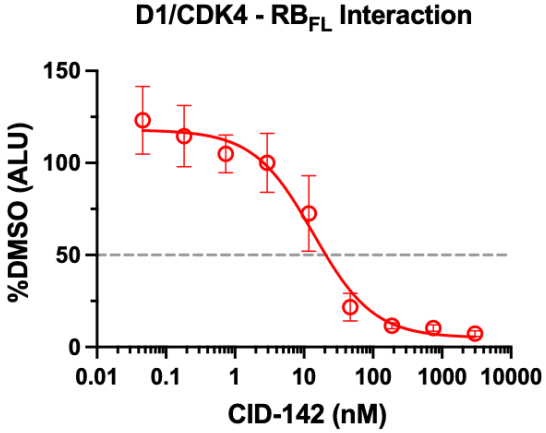
Papers on “CDK6 escape”

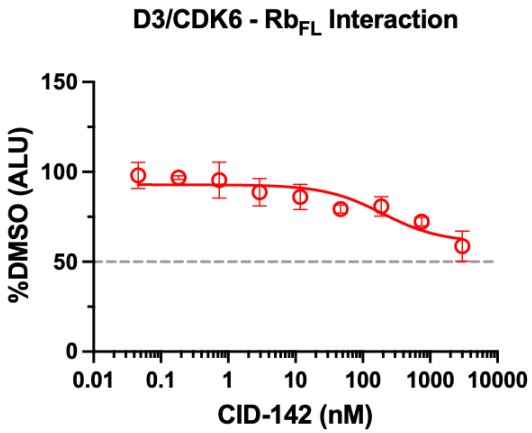
Yang et al., Oncogene 2017
Li et al., Cancer Cell 2018
O’Leary et al., Cancer Discovery 2018
Griffiths et al., Nat Cancer 2021
Li et al., Cancer Discovery 2022
Haines, Shapiro et al., Oncotarget 2018
Cornell, Shapiro et al., Cell Rep 2019

An advanced compound selectively inhibits cyclin D1 over D3









Alpha-screen:
Cell-free detection of interaction between cyclin D and Rb.

NanoBiT:
In-cell detection of interaction between cyclin D and Rb.

Advanced compound inhibits D1-driven heme and ER+ breast cancer cell-lines

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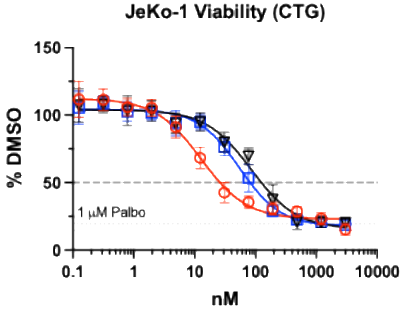
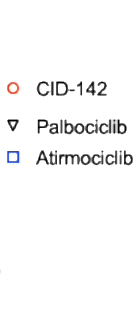
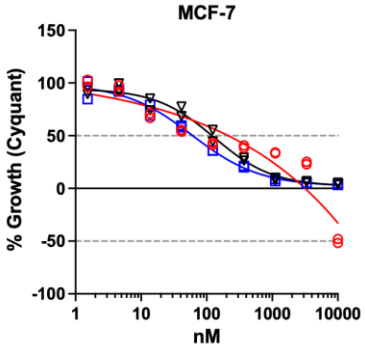
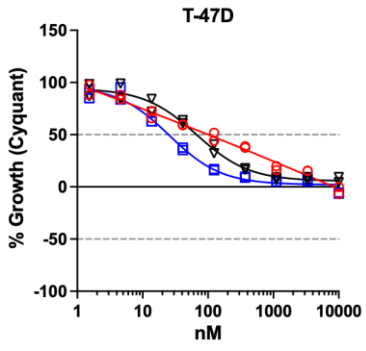
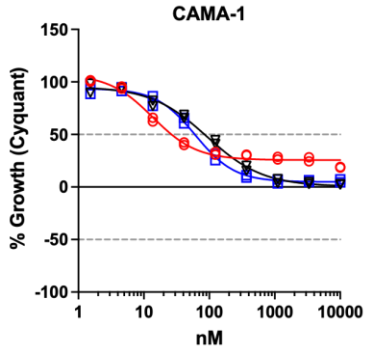
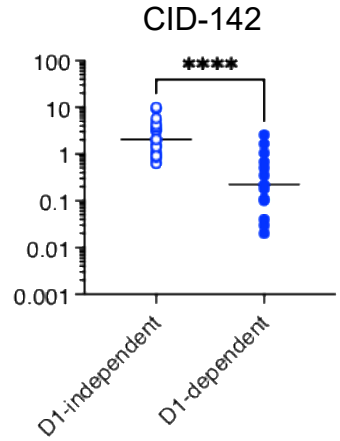


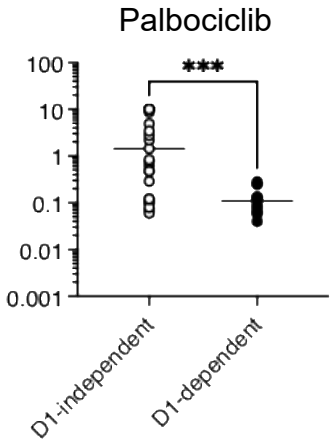


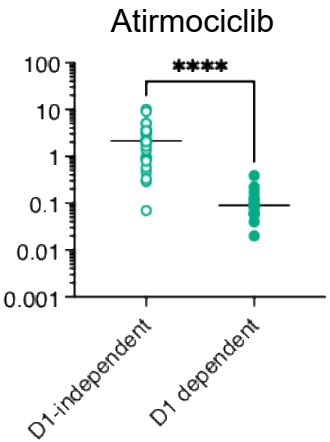










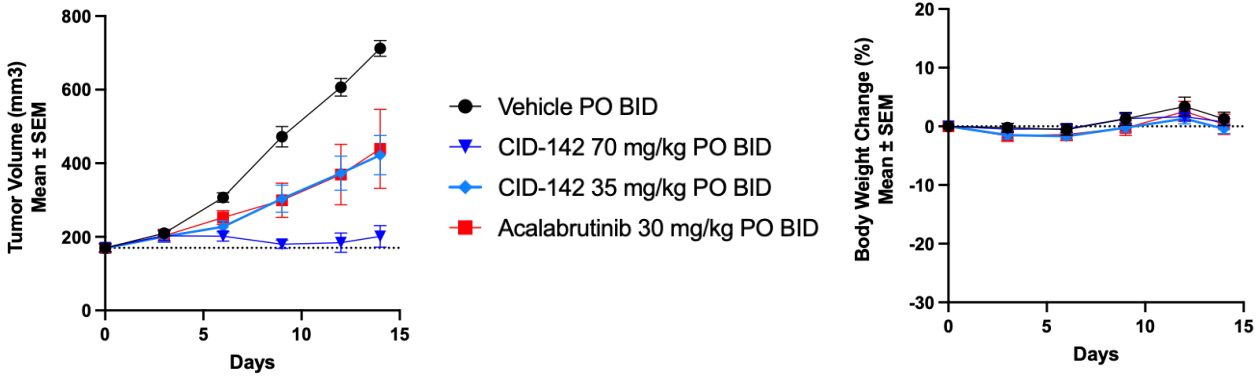


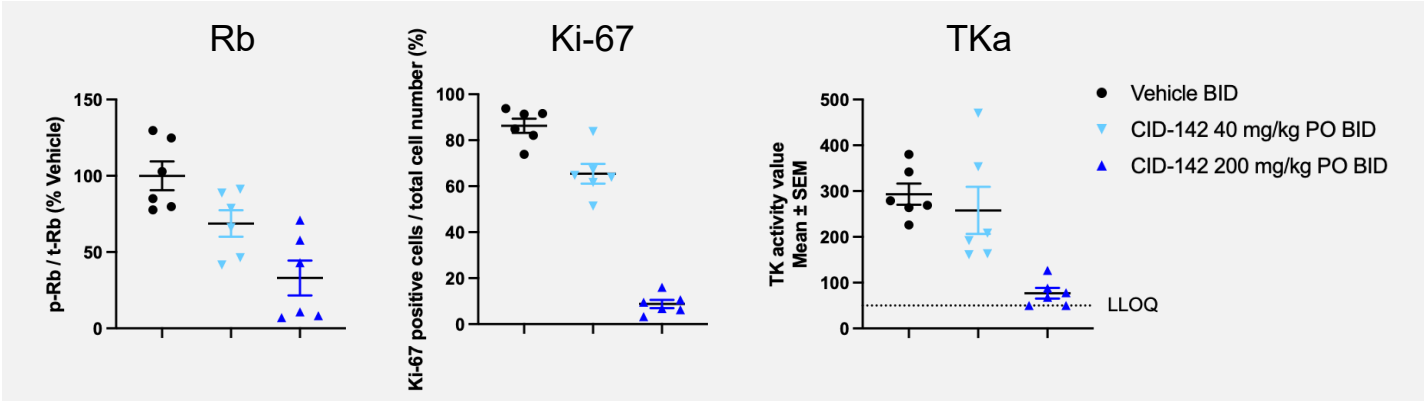
Confirmed to occur via **dose-dependent arrest of cells in G1-phase.**

(EdU incorporation assay in Jeko-1)

Advanced compound inhibits tumor growth in cell-line derived xenograft mouse model of mantle cell lymphoma

JeKo-1: CCND1 t(11;14) MCL





Transforming the treatment of cancer with industry-leading macrocycle platform and first-in-class pipeline of cyclin-targeted therapies

AACR American Association for Cancer Research Annual Meeting April 17-22, 2026 SAN DIEGO
AACR.ORG/AACR2026 | #AACR26

Advancing the only cyclin franchise in biopharma

First-in-class cyclin A/B RxL inhibitor initiating dose expansion in mid-2026 (NCT06577987)

First-in-class cyclin D1 RxL inhibitor on-track for IND filing by YE 2026

First-in-class platform-generated inhibitors of undisclosed cyclin, partnered with Boehringer Ingelheim

Orally bioavailable macrocyclic peptides are a powerful modality for inhibiting previously undruggable intracellular protein-protein interactions.

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