IAM-C1, a Potent and Selective Dual CDK2/CDK4 Inhibitor, Demonstrates Robust Antitumor Activity and a Favorable Preclinical Tolerability Profile

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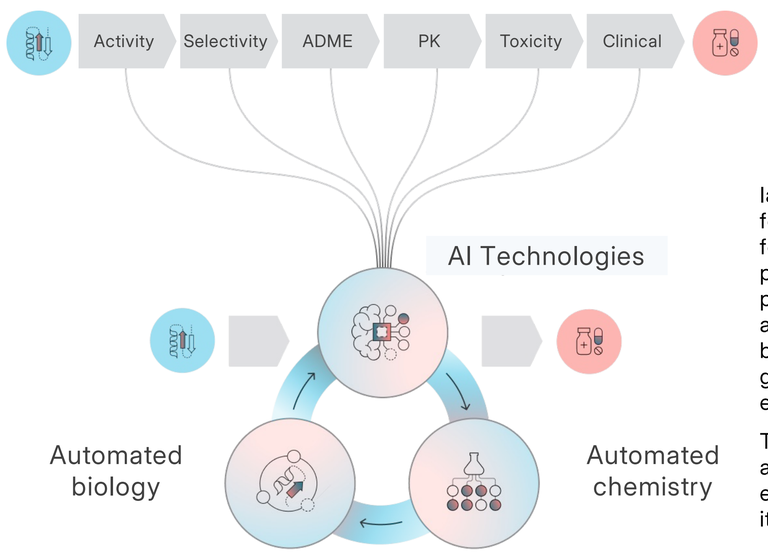
Background

The clinical benefit of CDK4/6 inhibitors in HR+/HER2- metastatic breast cancer validates G1/S cell cycle control as a therapeutic strategy. However, intrinsic and acquired resistance remain important limitations. High CCNE1 expression, through increased CDK2 signaling, has been implicated in both primary and acquired resistance to CDK4/6 inhibitors in HR+/HER2– breast cancer, supporting the rationale for targeting both CDK4/cyclin D and CDK2/cyclin E signaling. Selective dual CDK2/CDK4 inhibition may therefore address diverse mechanisms of G1/S dysregulation while sparing CDKs associated with dose-limiting toxicities. IAM-C1 is a selective dual CDK2/CDK4 inhibitor under development for cancers characterized by dysregulated CDK2 and/or CDK4 activity, including HR+/HER2- breast cancer and CCNE1-amplified cancers.

Key takeaways

- IAM-C1 potently and selectively inhibits CDK2/CDK4, suppressing RB phosphorylation, cell-cycle progression, and proliferation across cancer cell lines with distinct CDK dependencies.
- IAM-C1 demonstrates broad antitumor activity across models with distinct CDK2 and CDK4 dependencies. In the CDK2/CDK4 co-dependent MFE-296 model, IAM-C1 achieves greater tumor growth inhibition than single-agent CDK2, CDK4, and CDK4/6 inhibitors and comparable efficacy to the combination of CDK2 and CDK4 inhibitors.
- In the CDK4/6 inhibitor-resistant ST4316B breast cancer PDX model, IAM-C1 achieved 78% TGI versus 24% with palbociclib.
- Combining IAM-C1 with fulvestrant or imlunestrant significantly enhances antitumor activity versus the respective SERD monotherapies in the ER+/HER2- MCF-7 breast cancer model.
- In rats, IAM-C1 showed minimal neutrophil reductions compared with combined selective CDK2/CDK4 inhibition, despite higher efficacious exposure multiples.
- IAM-C1 IND filing is planned for Q4 2026.

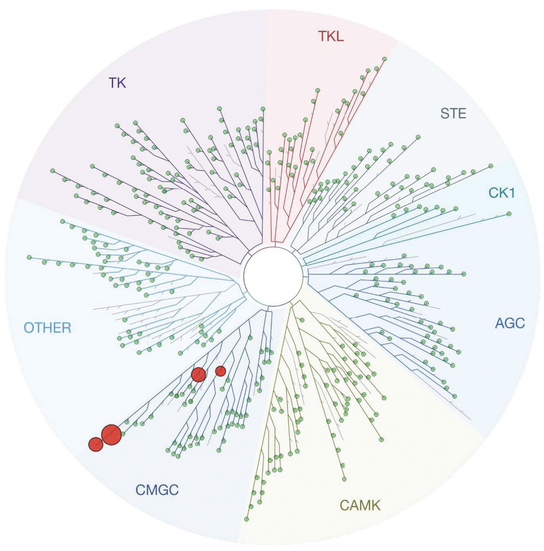
Figure 1 IAM-C1 discovery enabled by Iambic's AI/ML models (Enchant and NeuralPLexer) and high-throughput experimental platform



Iambic's molecular superintelligence platform integrates advanced AI technologies featuring Enchant, for multimodal end-point prediction, and NeuralPLexer for protein-ligand structural predictions, with automated experimental chemistry and biology capabilities as one unified system, guiding the design and prioritization of experiments.

The interplay of Enchant, NeuralPLexer and automated laboratory data generation enables fast validation of hypotheses and iterative refinement of models.

Figure 2 IAM-C1 is a potent CDK2/CDK4 dual inhibitor and is highly selective across the kinome



IAM-C1 biochemical potency
CDK2/CCNE1 IC50 < 1 nM
CDK4/CCND1 IC50 < 1 nM

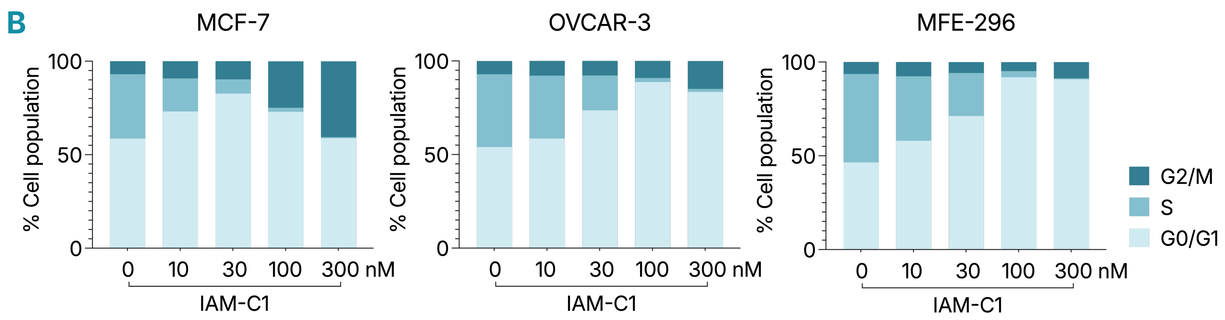
Broad kinome selectivity of IAM-C1 was assessed using the Eurofins KINOMEscan™ scanMAX panel. At 30 nM, four non-mutant off-target kinases met the binding-hit criterion of percent of control below 35%.

Figure 3 IAM-C1 potently inhibits cancer cell proliferation, suppresses RB phosphorylation and depletes S-phase cells

A

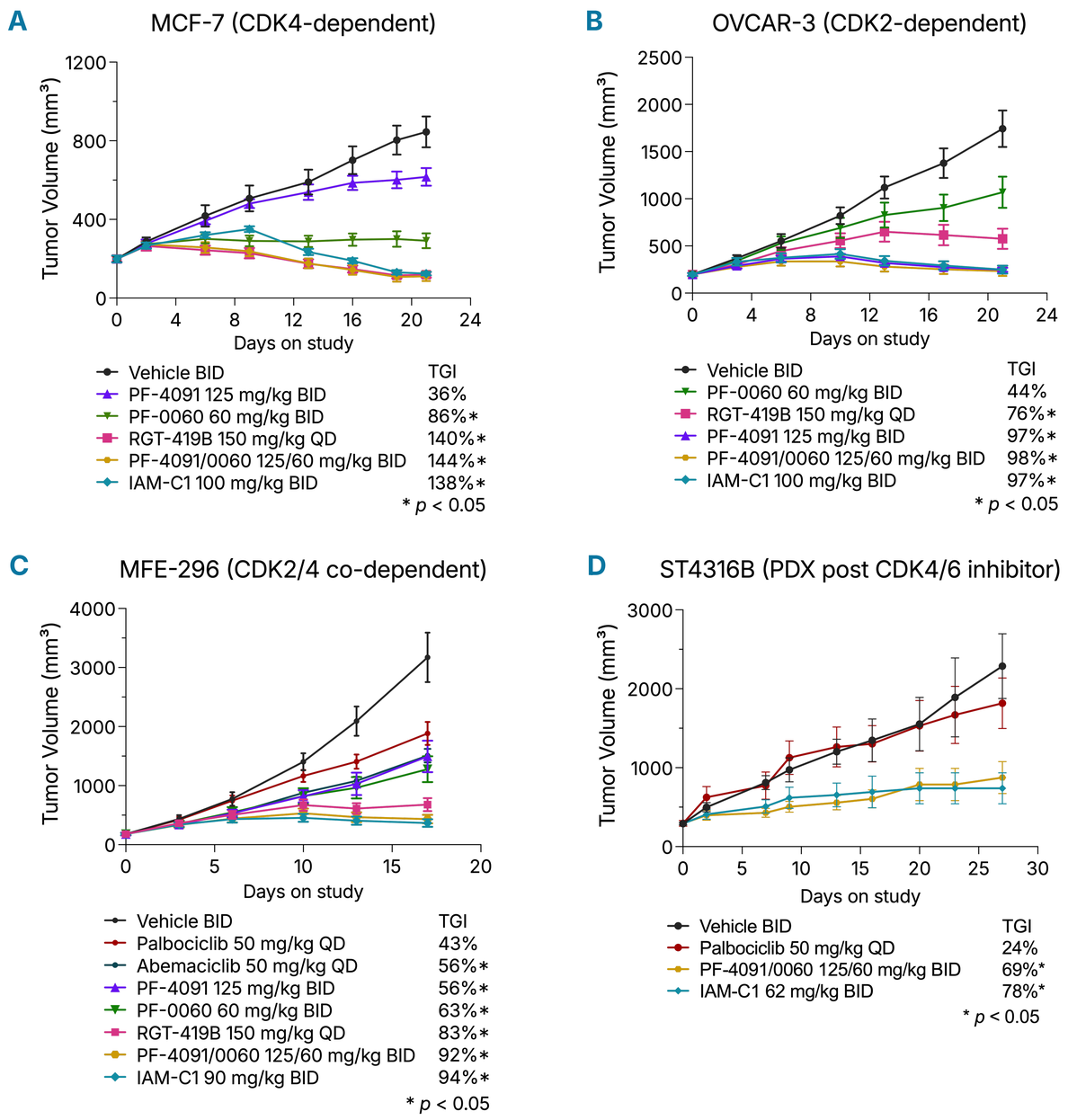
Assays	Cancer cell model	MCF-7	OVCAR-3	MFE-296
	Cell line dependency	CDK4	CDK2	CDK2/CDK4
6-day CyQuant IC_{50} (nM)	PF-4091 (CDK2 inhibitor)	880	140	900
	PF-0060 (CDK4 inhibitor)	320	3700	570
	PF-4091/0060 1:1	230	290	150
	IAM-C1 (CDK2/CDK4 dual inhibitor)	50	100	40
pRB (Ser807/811) IC_{50} (nM)	PF-4091 (CDK2 inhibitor)	3600	39	>10000
	PF-0060 (CDK4 inhibitor)	47	720	160
	PF-4091/0060 1:1	130	92	120
	IAM-C1 (CDK2/CDK4 dual inhibitor)	19	19	18

B



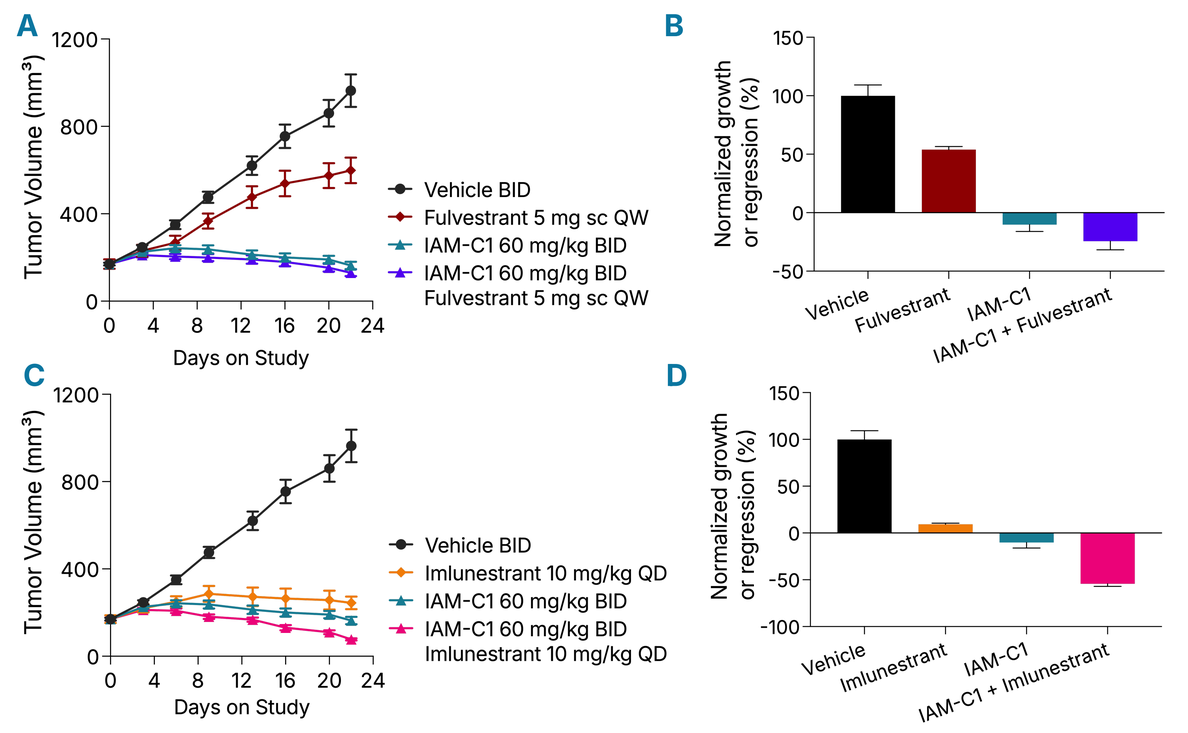
A. Tool compounds were used to establish and confirm CDK2 and CDK4 dependencies of cancer cell lines MCF-7, OVCAR-3 and MFE-296. IC_{50} of the combination was expressed as the total concentration of the two compounds. MCF-7, ER+/HER2- breast cancer; OVCAR-3, CCNE1-amplified ovarian cancer; MFE-296, endometrial cancer.
B. The effects of IAM-C1 on cell-cycle were evaluated using 5-ethynyl-2′-deoxyuridine (EdU) incorporation and DNA-content flow cytometry following 24 hours of treatment. PF-4091 = PF-07104091, PF-0060 = PF-07220060.

Figure 4 IAM-C1 demonstrated broad antitumor activity as a single agent across CDK2-, CDK4- and CDK2/4-dependent models and in a CDK4/6 inhibitor-resistant ER+/HER2- breast cancer PDX model



A-C. The antitumor efficacy of IAM-C1 was evaluated in CDX models MCF-7, OVCAR-3 and MFE-296 in female BALB/c nude mice. For MCF-7 model, mice were implanted subcutaneously with a 17β-estradiol pellet (0.5 mg, 90-day release) one day before cell inoculation. Treatment groups were compared to vehicle control using a two-way mixed-effects model with time as the repeated factor. **D.** ST4316B patient-derived xenograft (PDX) model (ER+/HER2-) was established from a patient with recurrent breast cancer previously treated with abemaciclib, palbociclib and radiation therapy. Efficacy was evaluated as the change in tumor volume from Day 0 (ΔTV) on the Day 27 endpoint (xenoSTART). Treatment groups were compared using a two-tailed one-way ANOVA with Dunnett's multiple-comparisons test versus vehicle control. PF-4091: CDK2 inhibitor PF-07104091; PF-0060: CDK4 inhibitor PF-07220060. RGT-419B: CDK4/2 inhibitor RG6794. All analyses were conducted in GraphPad Prism, and $p < 0.05$ was defined as statistically significant.

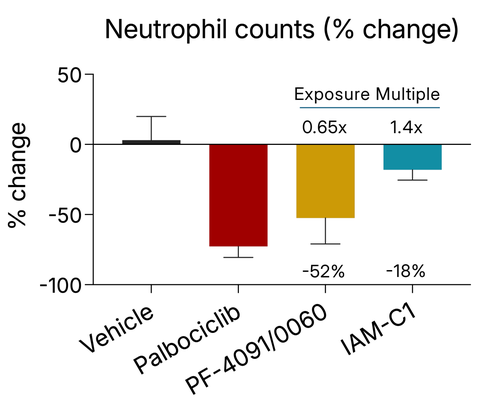
Figure 5 IAM-C1 demonstrates increased anti-tumor activity when combined with fulvestrant and imlunestrant in the MCF-7 xenograft model



Antitumor activity of IAM-C1 was evaluated alone or in combination with fulvestrant **(A-B)** or imlunestrant **(C-D)**. Tumor growth curves are shown in **A/C** whereas normalized tumor growth/regression (right panel, %) is shown in **B/D** and expressed as the mean ± SEM (n=8) of either the percent of mean vehicle growth for growing tumors or the percent change from baseline for regressing tumors, respectively. p <0.05 IAM-C1+fulvestrant vs fulvestrant alone; IAM-C1+imlunestrant vs imlunestrant and IAM-C1 alone. Statistical analysis was performed in PRISM using two-way ANOVA and Dunnett's multiple comparisons test with each combination arm as the reference group **(A,C)**.

Figure 6 IAM-C1 exhibits a favorable hematology profile in rat

A



B

Compound	% change neutrophil
Vehicle	2.8 (-1.7[a], 7.1[b], 3.0[c])
Palbociclib (100 mg/kg QD)	-69 (-66[a], -69[b], -73[c])
PF-4091/0060	-48 (-43[a], NA[b], -52[c])
IAM-C1	-13 (NA[a], -7.5[b], -18[c])

Repeated oral dosing of IAM-C1 exhibits a minimal effect on neutrophil counts in male rats. **A.** Representative study (n=5/group; n=4 for PF-4091/0060 due to tolerability). Exposure multiple = steady-state unbound rat $AUC_{0\text{-}24h}$ / efficacious steady-state unbound mouse $AUC_{0\text{-}24h}$ (MFE-296 model). For PF-4091/0060, the mean of individual compound exposure multiples was used. **B.** Mean neutrophil count changes across study cohorts (a: 14 days; b: 12 days; c: 13 days). Exposure multiples: PF-4091/0060, 0.75× (a) and 0.65× (c); IAM-C1, 1.3× (b) and 1.4× (c). NA, not tested.

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