IAM217: a Novel, Brain-penetrant KIF18A Inhibitor for Targeting Chromosomal Instability in Cancer

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Background

Chromosomal instability (CIN), a hallmark of cancer linked to poor prognosis, creates a selective dependence on mitotic control mechanisms that are required to enable accurate chromosome alignment. KIF18A, a kinesin motor protein that stabilizes chromosome positioning at the metaphase plate, is critical for this process. In CIN-high tumors, KIF18A inhibition is disruptive to chromosome alignment, causing prolonged mitotic arrest, centrosome fragmentation, micronucleation, and apoptosis, while largely sparing normal diploid cells. This selective vulnerability makes KIF18A an attractive therapeutic target in cancer.

IAM217 is a novel, potent, and selective small-molecule KIF18A inhibitor with differentiated preclinical properties relative to other KIF18A inhibitors currently in clinic. IAM217 in vivo efficacy was assessed in a panel of cell line-derived and patient-derived xenograft models, resulting in deep regressions in multiple models.

Pharmacodynamic biomarkers, with plasma and tumor PK indicate strong correlation between drug exposure, PD response and efficacy. Furthermore, IAM217 achieved deep regression in an orthotopic brain efficacy study, indicating potential for benefit in patients with brain metastasis.

Targeting KIF18A with IAM217 may provide a novel anti-cancer treatment option for patients with potential to reduce tumor burden from brain metastasis. These data support the continued development of IAM217 as a therapeutic strategy for CIN-high cancers.

Figure 1. Tumor Cells with CIN Require KIF18A for Proliferation

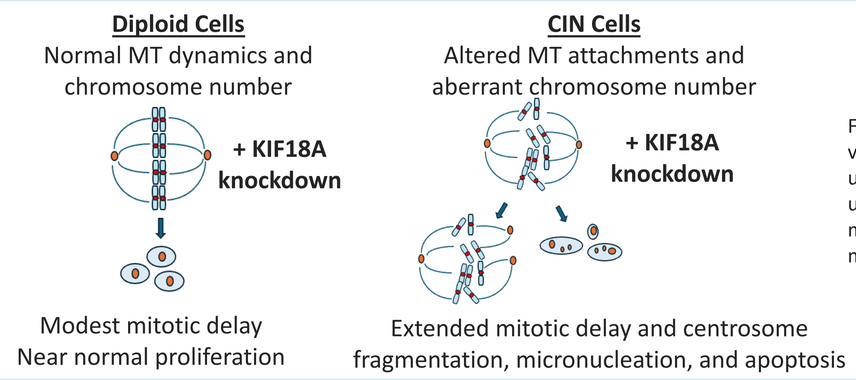
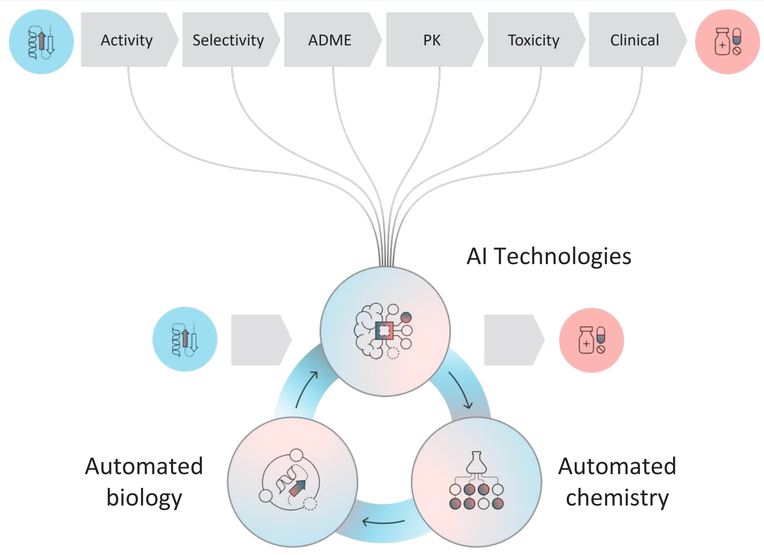


Figure 1. KIF18A is a mitotic vulnerability in chromosomally unstable cancers. CIN cells are uniquely dependent on KIF18A-mediated chromosome alignment and metaphase to anaphase transition.

Figure 2. 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 endpoint 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.

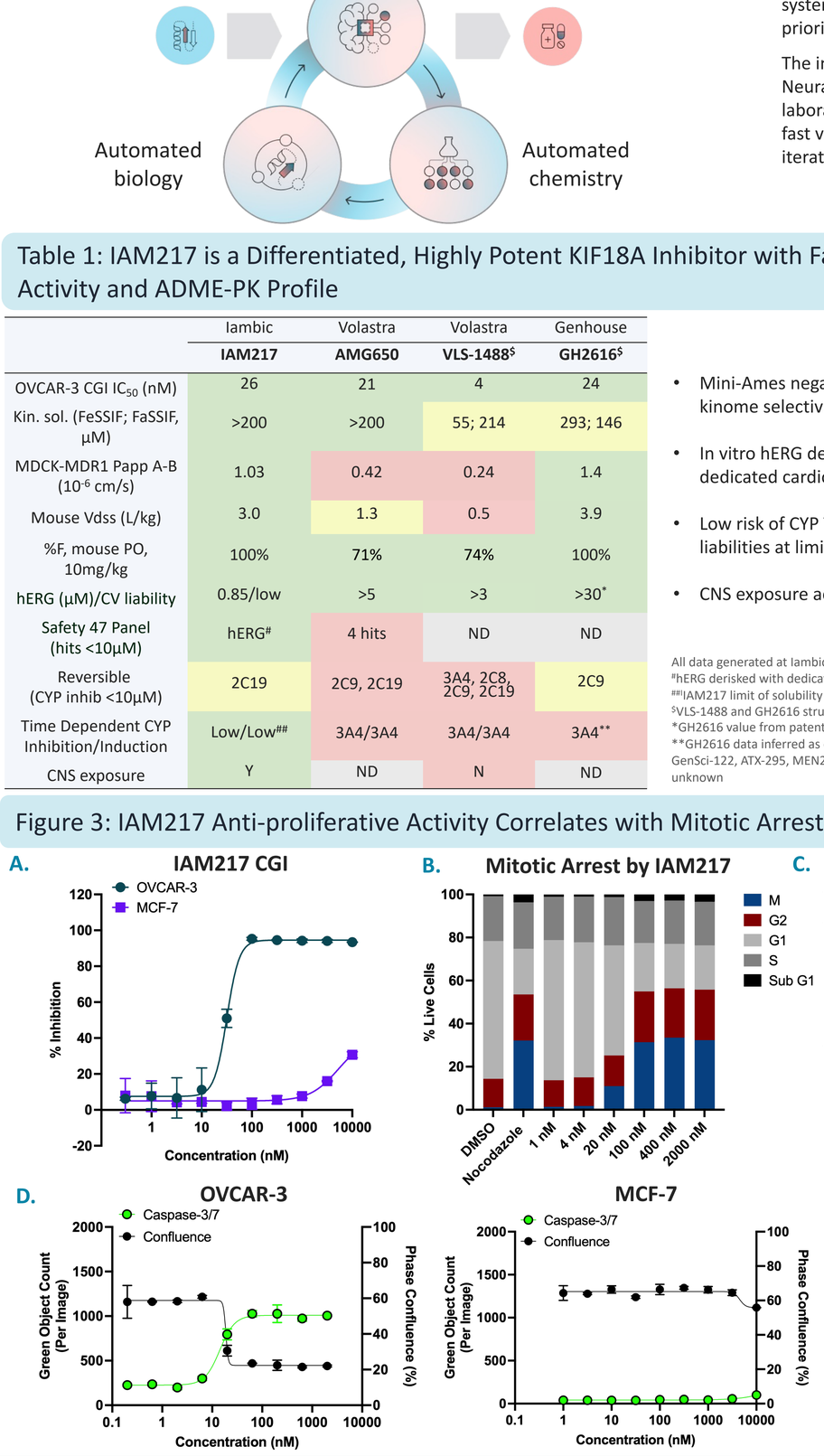
Table 1: IAM217 is a Differentiated, Highly Potent KIF18A Inhibitor with Favorable In Vitro Activity and ADME-PK Profile

	Iambic	Volastra	Volastra	Genhouse
	IAM217	**AMG650**	**VLS-1488$**	**GH2616$**
OVCAR-3 CGI IC_{50} (nM)	26	21	4	24
Kin. sol. (FeSSIF; FaSSIF, µM)	>200	>200	55; 214	293; 146
MDCK-MDR1 Papp A-B (10^{-6} cm/s)	1.03	0.42	0.24	1.4
Mouse Vdss (L/kg)	3.0	1.3	0.5	3.9
%F, mouse PO, 10mg/kg	100%	71%	74%	100%
hERG (µM)/CV liability	0.85/low	>5	>3	>30*
Safety 47 Panel (hits <10µM)	hERG#	4 hits	ND	ND
Reversible (CYP inhib <10µM)	2C19	2C9, 2C19	3A4, 2C8, 2C9, 2C19	2C9
Time Dependent CYP Inhibition/Induction	Low/Low##	3A4/3A4	3A4/3A4	3A4**
CNS exposure	Y	ND	N	ND

- Mini-Ames negative; clean kinesin and kinome selectivity screen
- In vitro hERG derisked by conducting dedicated cardiovascular studies in dogs
- Low risk of CYP TDI and induction liabilities at limit of solubility
- CNS exposure achieved in rodents

All data generated at Iambic unless otherwise indicated.
#hERG derisked with dedicated telemetrized dog CV study
##IAM217 limit of solubility reached at 5uM in standard assay conditions
$VLS-1488 and GH2616 structure inferred from patent applications
*GH2616 value from patent WO 2024/002328 A1
**GH2616 data inferred as clinical protocol excludes substrates of 3A4
GenSci-122, ATX-295, MEN2501 also now on clinicaltrials.gov; structures unknown

Figure 3: IAM217 Anti-proliferative Activity Correlates with Mitotic Arrest and CIN Status



C. Cell-type Specific Inhibition

Assay	IAM217 IC_{50}
MCF-7 (low CIN)	> 10000 nM
OVCAR-3 (high CIN)	24 nM
CFU-Erythroid	>10000 nM
CFU-GM	7700 nM

Figure 3. (A) Cell growth inhibition with IAM217 dose response in OVCAR-3 vs MCF-7. (B) Mitotic arrest in OVCAR-3 as measured by pHH3 staining. (C) The selective potency of IAM217 is reflected in the lack of in vitro toxicity in normal cells and bone marrow hematopoietic progenitor cells. (D) Quantification of apoptosis and confluence induced by IAM217 in CIN-high OVCAR-3 and CIN-low MCF-7 cells.

Figure 4: IAM217 Demonstrates Dose-proportional Increase in Total Plasma Exposure that Correlates with Dose-dependent Increase in Antitumor Activity, and is Well Tolerated

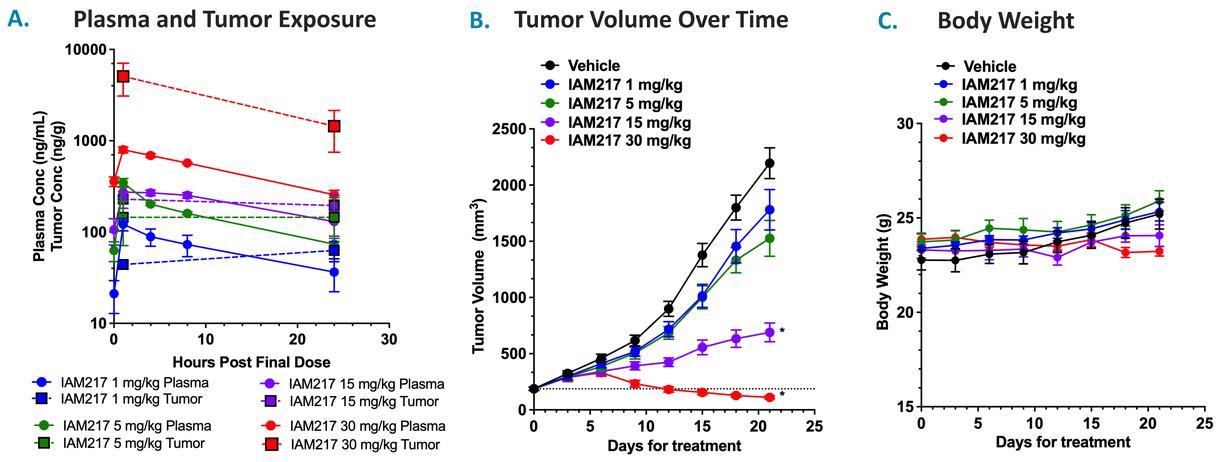


Figure 4. (A) Mice bearing OVCAR-3 tumors were orally administered IAM217 dose response once daily for 21 days. Plasma and tumor PK evaluation demonstrates dose dependent exposures achieved. (B) IAM217 treatment resulted in dose dependent increase in TGI which correlated to plasma and tumor PK and (C) was well tolerated at all dose levels. * indicates $p < 0.05$.

Figure 5: IAM217 Achieves Dose-proportional Increase in Plasma Exposure that Correlates with Dose-dependent Increase in Anti-tumor Activity, Mitotic Arrest and Apoptosis

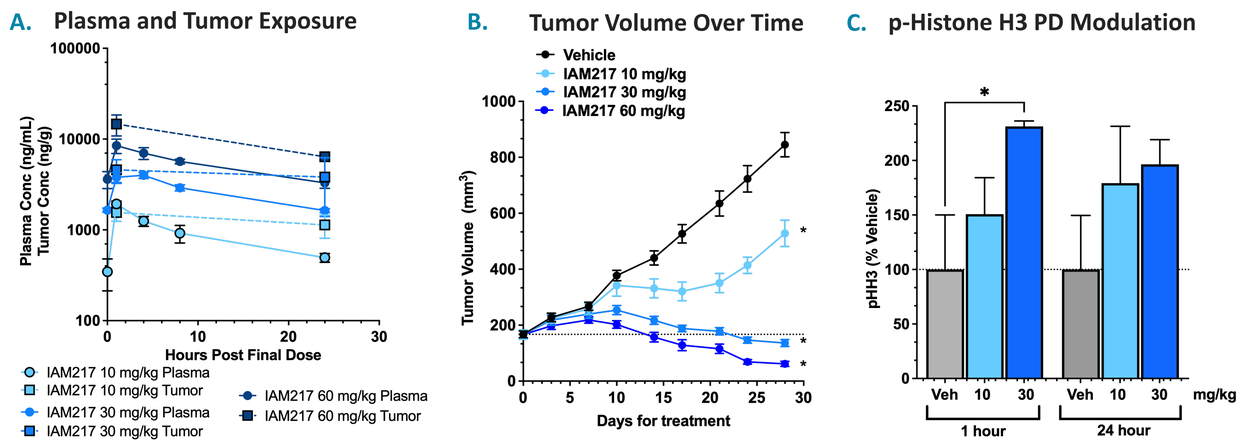


Figure 5. (A) Mice bearing OVCAR-8 tumors were orally administered IAM217 dose response once daily for 28 days. Plasma and tumor PK evaluation demonstrates dose dependent exposures achieved. (B) IAM217 treated resulted in dose dependent increase in TGI which correlated to plasma and tumor PK and (C) achieved dose dependent modulation of phospho-Histone H3, indicating mitotic arrest with IAM217 treatment. * indicates $p < 0.05$.

Figure 6: IAM217 Achieves Deep Regressions Across Multiple Xenograft Models

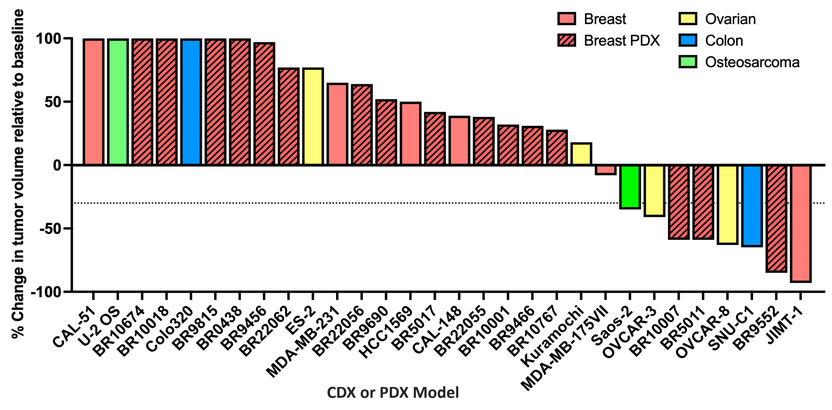


Figure 6. IAM217 at 60 mg/kg QD for ~ 21 days results in robust anti-tumor activity across a panel of breast cell-line derived (CDX) and patient-derived (PDX) xenograft models, as well as ovarian, colon and osteosarcoma CDXs.
Crown Bioscience supported the efficacy studies in PDX models.

Figure 7: IAM217 Exceeds Free IC_{90} and Demonstrates Efficacy in Intracranial Model

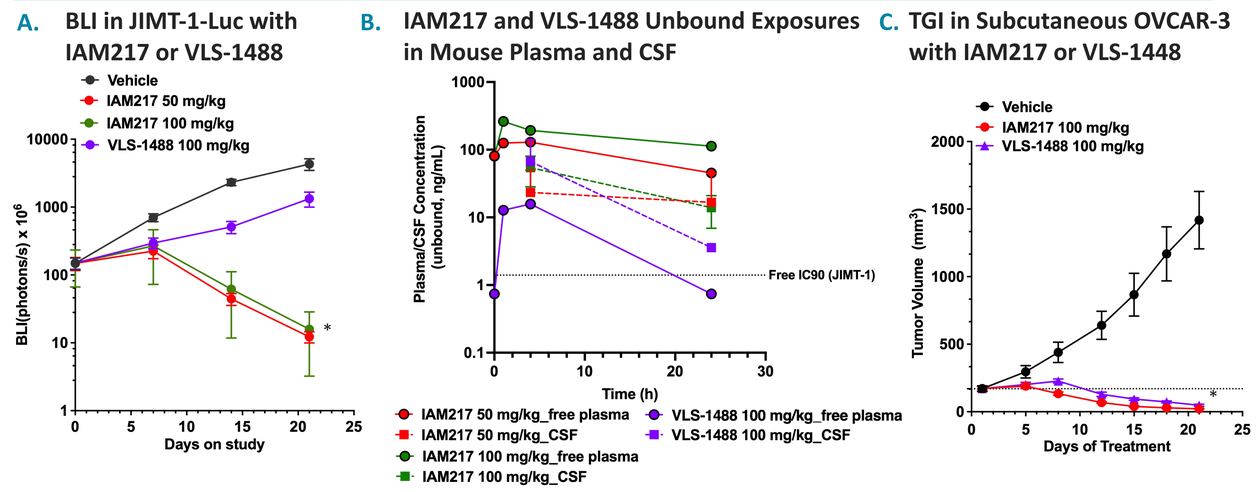


Figure 7. (A) IAM217 achieves -90% regression in JIMT-1-Luc breast cancer model implanted intracranially via stereotactic injection, indicating potential for benefit in patients with brain metastasis. VLS-1488 does not lead to regression. * indicates $p < 0.05$.
(B) IAM217 unbound plasma and CSF concentrations exceed free IC_{90} for over 24 hours. Dotted line indicating free IC_{90} represents both IAM217 and VLS-1488. (C) IAM217 and VLS-1488 drive deep regressions in the OVCAR-3 xenograft model implanted subcutaneously.

Figure 8: In vitro IAM217 and Eribulin Combination Shows Evidence of Synergy

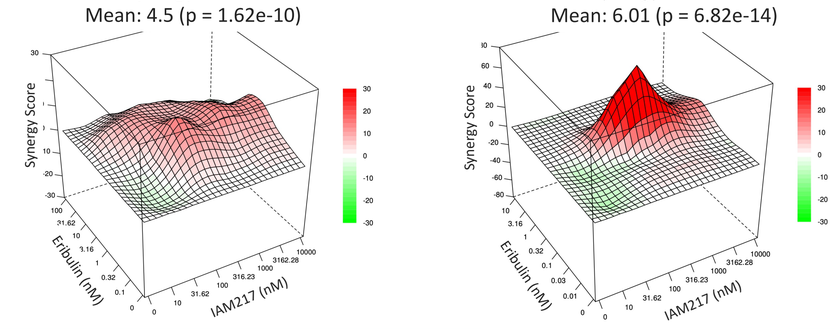


Figure 8. (A) To evaluate initial combination potential of IAM217 with SOC in specific tumor types, Kuramochi (ovarian cancer) cell line was treated with a dose response of both IAM217 and eribulin for 6 days. Areas in red highlight synergy by HSA.
(B) HCC1187 (TNBC) cell line treated with IAM217 + eribulin for 6 days as above. Areas in red highlight synergy by HSA.

Conclusions

- IAM217 is a potent and differentiated KIF18A inhibitor with selective activity in tumor cells with chromosomal instability
- IAM217 is well tolerated and exhibits dose-dependent plasma and tumor levels that correlate well with tumor regression
- IAM217 demonstrates robust anti-tumor activity across a broad spectrum of breast and ovarian xenograft models
- IAM217 reduces tumor burden in an intracranial mouse model of brain metastasis
- IAM217 in combination with an approved microtubule inhibitor demonstrates synergy in ovarian and TNBC cell lines in vitro
- These data support the continued development of IAM217 as a therapeutic strategy for CIN-high cancers, including in patients with brain metastases. IND submission accepted.

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