Activity of the Novel KIF18A Inhibitor, ATX-295, is Enriched in Whole Genome Doubled Ovarian and TNBC Preclinical Models

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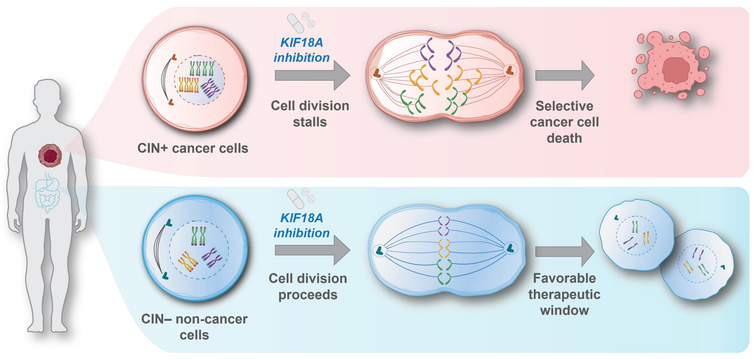
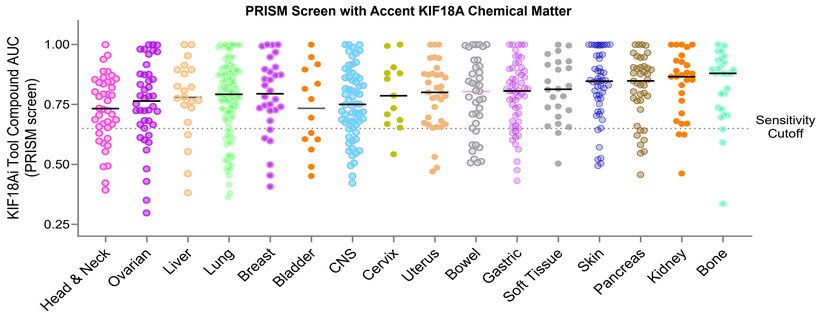
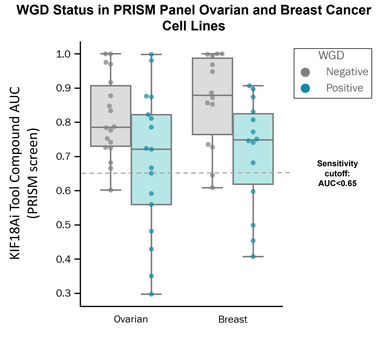
Mitotic Kinesin KIF18A is a Selective Vulnerability in Chromosomally Instable (CIN) Tumors

- KIF18A is a plus-end directed kinesin that facilitates chromosome alignment and spindle microtubule dynamics during mitosis[1]
- Cells with ongoing chromosomal segregation defects are vulnerable to disrupted mitosis when KIF18A is lost; thus, KIF18A is a compelling synthetic lethal target in chromosomally instable (CIN+) cancers[2,3,4,5,6]
- In an 826 cell line PRISM screen, 18% of cell lines were sensitive to KIF18A inhibition, with a high proportion of sensitivity in CIN high indications such as ovarian, breast, and lung cancer
- ATX-295, a proprietary Accent Therapeutics KIF18A inhibitor currently undergoing clinical testing, induced mitotic arrest, G2/M accumulation, and apoptosis in CIN+ but not CIN- ovarian and triple negative breast cancer cell lines
- ATX-295 potently inhibited proliferation in a panel of high grade serous ovarian (HGSOC) and triple negative breast cancer (TNBC) cell lines; sensitivity is enriched in cells positive for whole genome doubling, a correlate of CIN
- ATX-295 treatment induced durable tumor growth inhibition in WGD+ ovarian cancer and TNBC PDX models
- These data identify WGD, a CIN surrogate, as a potential biomarker of ATX-295 sensitivity in ovarian cancer models, and further validate KIF18A as a synthetic lethal vulnerability in CIN+ tumors



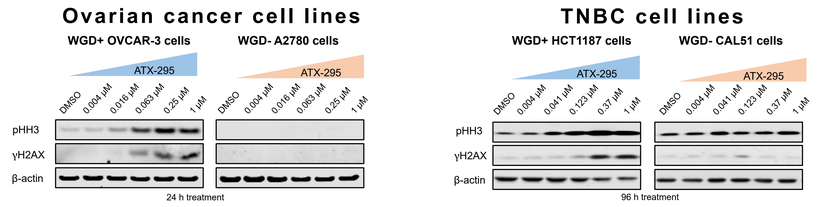
KIF18A Inhibition: Large Patient Opportunity Across Multiple Solid Tumor Indications



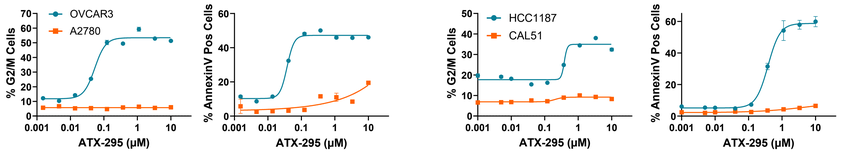


- The *in vitro* activity of a proprietary Accent tool compound was evaluated across multiple indications in a PRISM screen
- 18% of 826 cell lines were KIF18A dependent, especially ovarian, breast, lung and head & neck cancer cell lines
- Whole genome doubling (WGD) identified a set of sensitive Ovarian and Breast cancer cell lines

ATX-295 Alters Microtubule Dynamics Leading to Mitotic Catastrophe & Cell Death in WGD+ Cancer Cell Lines

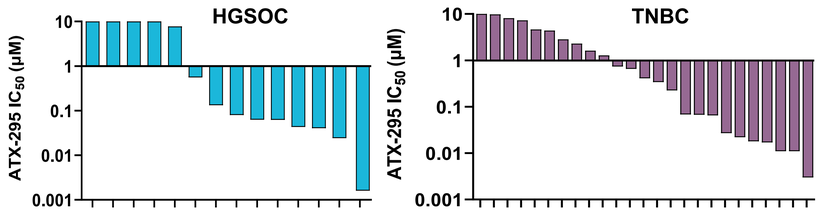


ATX-295 Induces Mitotic Arrest and Apoptosis in WGD+ Cells



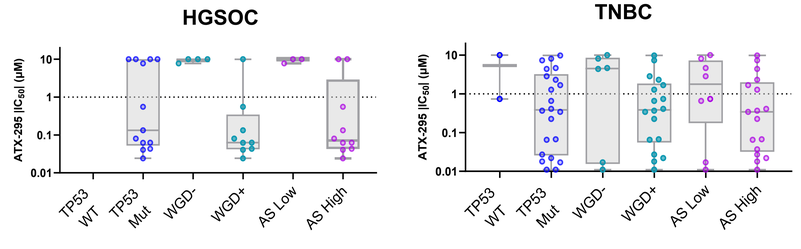
- ATX-295 is a potent and selective proprietary Accent Therapeutics clinical candidate, and inhibits KIF18A biochemical activity with an IC_{50} of 16 nM
- ATX-295 disrupts mitotic spindle dynamics leading to dose-dependent induction of p-HH3 and γH2AX in WGD+ OVCAR-3 and HCC1187 cells, consistent with cells arresting in mitosis due to dependency on KIF18A for M phase progression
- WGD- A2780 or CAL51 cells, which are not dependent on KIF18A, do not exhibit elevated γH2AX, consistent with the lack of dependence on KIF18A in this cell line
- G2/M arrest and apoptosis are induced in a dose-dependent manner upon ATX-295 treatment of WGD+ OVCAR-3 or HCC1187 cells but not in WGD- A2780 or CAL51 cell lines

ATX-295 Exhibits Robust Anti-Proliferative Activity in HGSOC and TNBC Cell Lines



- 64% (9 out of 14) of HGSOC cell lines are sensitive to ATX-295; 56% (14 out of 25) of TNBC cell lines are sensitive to ATX-295
- These results are consistent with the elevated chromosomal instability observed in HGSOC and TNBC tumors[3]

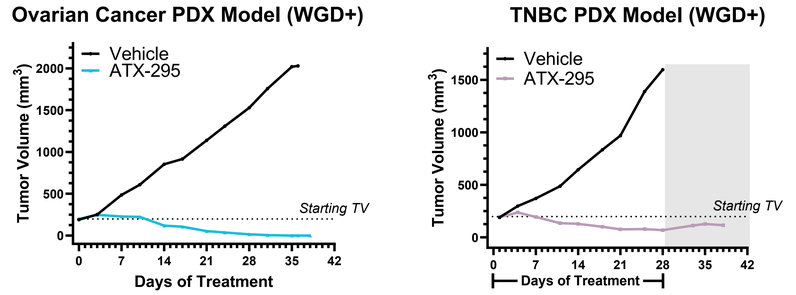
Correlates of CIN Enrich for KIF18A Dependence in Ovarian and Triple Negative Breast Cancer Cell Lines



AS = aneuploidy score
WGD = whole genome doubling
..... = sensitivity cutoff

- Genomic correlates of CIN, such as aneuploidy score or whole genome doubling, are enriched in HGSOC cell lines that are dependent on KIF18A
- A similar enrichment of ATX-295 sensitivity is observed in CIN+ TNBC cell lines

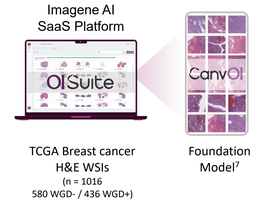
ATX-295 Induces Robust Tumor Growth Inhibition in WGD+ PDX Models

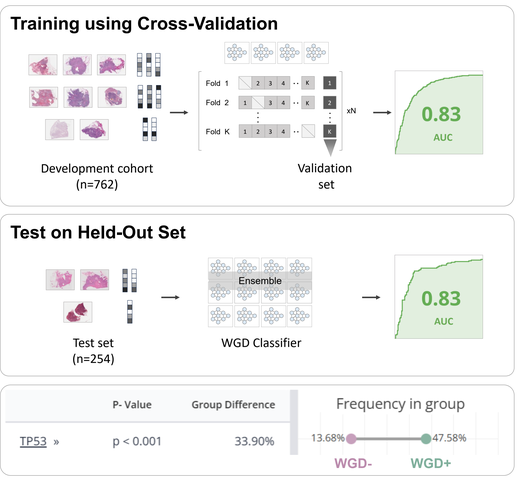


- Oral dosing of ATX-295 leads to durable tumor regression in the WGD+ Ovarian and TNBC PDX models
- ATX-295 was well tolerated with no changes in body weight

Combination of Molecular Pathology and AI Reveals Opportunities for WGD Detection in Clinical Samples

WGD classifier Development and Testing





- The WGD classifier was independently developed and validated within minutes on the OI Suite platform, using a fully no-code workflow, achieving an AUC of 0.83 on a held-out test set
- TP53 mutations were enriched in WGD+ predicted samples, consistent with known biology[3]
- These results demonstrate proof-of-concept for AI-based WGD detection in clinical samples

Conclusions

- A large cell panel screen demonstrates the potential for KIF18A inhibition across multiple solid tumor indications with high CIN, like ovarian, breast, lung, and head & neck
- ATX-295 is a selective KIF18A inhibitor that leads to mitotic arrest and apoptosis due to DNA damage and malformed mitotic spindles in CIN+ cells
- Whole genome doubling, a CIN surrogate, is predictive of ATX-295 sensitivity, *in vitro* and *in vivo* as demonstrated in an ovarian cancer and TNBC cell line panel and in PDX models
- AI-based detection of WGD from patient H&E-stained tissue slides[8] demonstrates promise as a tool for identifying patients most likely to respond to ATX-295 therapy
- For more info on our current clinical trial, please visit *ClinicalTrials.gov* ID: NCT06799065

Acknowledgements & References

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