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Sensitivity of Triple Negative Breast Cancer Cell Lines to PCM-075, a Highly Selective Polo-like Kinase 1 Inhibitor

Abstract #1468

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Background

- Triple negative breast cancer (TNBC) remains a significant challenge due to its aggressive nature and lack of therapeutic options beyond chemotherapy
- Molecular identification of TNBC subtypes enables clinical evaluation of targeted therapies, for example, PARP inhibitors (e.g. olaparib), and androgen receptor/synthesis (AR) inhibitors (e.g. bicalutamide, enzalutamide, and abiraterone)
- Polo-like Kinases (PLKs), a family of serine-threonine kinases, regulate various cellular processes including mitosis, DNA replication, and the stress response
- PLK1:
  - Over-expressed in many malignancies, including breast cancer
  - Inhibition induces cell-cycle arrest and apoptosis in cancer cell lines and xenograft tumor models
- PCM-075:
  - Orally-available, highly-selective PLK1 inhibitor
  - Causes G2/M arrest and apoptosis in highly mitotic cells
  - Kills taxol resistant cells and synergizes with taxol and the platinum-based antineoplastic, cisplatin
- PCM-075 is currently under clinical investigation.

Objective

- To evaluate the activity of PCM-075 in breast cancer cell lines, identify disease subtypes and potential drug combinations where PCM-075 may enhance the efficacy of current and future standard-of-care therapies

Methods

Sensitivity (IC_{50}) ~ Gene Expression
6 compounds that target PLK1
40 shared breast cancer cell lines
18,541genes[1]
Rank Correlation

↓

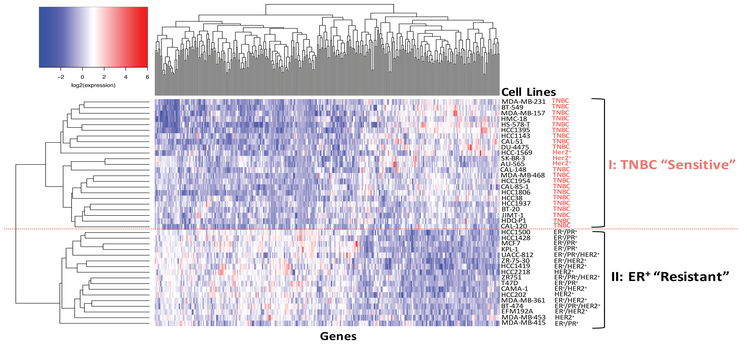
Identify gene expression signature broadly associated with sensitivity to PLK1 inhibition
Combine p-values (yields 350 genes)

↓

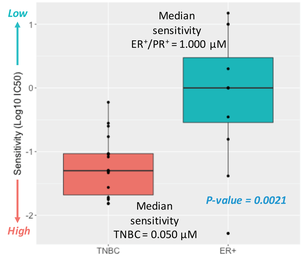
Correlate PLK1 inhibition associated gene expression signature with breast cancer cell lines types[2-5]
Heat Map/Cluster

Results

Clustering of cell lines by 350 genes that are associated with sensitivity naturally identifies a TNBC and an ER+ cluster. HER2+ cell lines occur in both clusters



TNBC cell lines are exquisitely sensitive to PCM-075



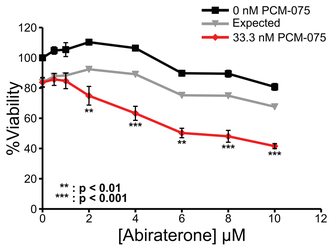
ER+/PR+	HER2+	Sensitive to PCM075 [IC50 < 0.1 µM] (N)
-	-	**14 (18)**
-	+	**2 (6)**
+	-	1 (7)
+	+	1 (5)

Multiple subtypes of TNBC cells are sensitive to PCM-075, including androgen receptor positive lines

Cell Line	TNBC Subtype	Histology	TP53 Status	AR?	PCM-075 (Sensitive IC50 < 0.1M)
HCC1143	Basal-like 1	DC	LOF	-	0.0274
HCC1937	Basal-like 1	DC	LOF	-	0.5955
MDA-MB-468	Basal-like 1	DC	LOF	**AR+**	**0.0828**
HCC1806	Basal-like 2	ASCC	LOF	-	0.0183
CAL851	Basal-like 2	IGA	LOF	-	0.0177
HDQP1	Basal-like 2	IDC	LOF	-	0.0509
DU4475	Basal-like IM	DC	WT	-	0.0465
HCC70	Basal-like 2	DC	LOF	-	0.2789
BT549	Mesenchymal-like	IDC	LOF	-	0.0486
CAL51	Mesenchymal-like	AC	WT	-	0.0191
MDA-MB-231	Mesenchymal-like	IDC	LOF	**AR+**	**0.1716**
HS578T	Mesenchymal-like	CS	LOF	-	1.0000
MDA-MB-436	Mesenchymal-like	IDC	-	-	0.0927
CAL-148	LAR	AC	LOF	**AR+**	**0.0154**
MDA-MB-453	LAR	AC	-	**AR+**	**0.0897**
MFM-223	LAR	AC	LOF	**AR+**	**0.0104**
BT-20	Unclassified	IDC	LOF	**AR+**	**0.0930**
HCC1395	Unclassified	DC	LOF	-	0.0494

IM = immunomodulatory; DC = ductal carcinoma; ASCC = acanthotylic squamous cell carcinoma; IGA = invasive galactophoric adenocarcinoma; IDC = inflammatory ductal carcinoma; AC = adenocarcinoma; CS = carcinosarcoma. [Based on Lehman *et al.*[3]
LOF = Loss of function/deleterious; WT = Wild Type; - = Unknown. [Based upon IARC TP53 Database[6]]
Androgen receptor status based on immunohistochemistry.[3]

PCM-075 and abiraterone demonstrate a marked synergy across doses in AR+ BT-20 cells



- Aberration is a selective, irreversible inhibitor of CYP17A1, and by extension androgen synthesis.
- Abiraterone is commonly used to treat castrate resistant prostate cancer and is under clinical investigation in breast cancer.

Conclusions

- TNBC / ER Negative breast cancer cell lines are exquisitely sensitive to PLK1 inhibition
- Sensitivity to PLK1 inhibition is correlated with underlying differences in gene expression
- Additional data is needed to understand the relevance of Her2 status to this observation
- PCM-075 sensitive TNBC cell lines include cells that express the androgen receptor (AR^+) and those which do not (AR^-)
- Sensitivity to inhibition of androgen synthesis by abiraterone is synergistically enhanced in the presence of mitotic inhibition by PCM-075
- Further investigation of the interaction between PCM-075 and abiraterone in both AR+ and AR- TNBC is ongoing
- These findings suggest that PCM-075 may represent a therapeutic option in TNBC, particularly in combination with other compounds with which it shows synergy, such as abiraterone

Literature & Notes

1. Cancer Therapeutics Response Portal [portals.broadinstitute.org/ctrp]
2. Hormone receptor status of each cell line established from literature and by clustering relative expression of ERBB2, ESR1, and PGR genes
3. Lehmann *et al.*, *J Clin. Invest.* 2011; 121(7): 2750-2767
4. Jiang *et al. BMC Genomics.* 2016; 17(Suppl 7): 525
5. Subik *et al. Breast Cancer (Aukl).* 2010; 4: 35-41
6. IARC TP53 Database [p53.iarc.fr]

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