Subtype and pathway specific responses to anti-cancer compounds in breast cancer

Heiser, et al.

Supplementary Information

Association of growth rate and response to therapeutic agents
In general, we found that luminal subtype cell lines grew more slowly than basal or claudin-low cells (Kruskal-Wallis test $p = 0.006$, Fig. S3A and Table S1) and the range of doubling times was broad (18 to 300 hours). This raised the possibility that the most sensitive cell lines were those that grew most rapidly. We tested this hypothesis by assessing the effects of subtype and doubling time simultaneously with an ANCOVA (see details below) and found that 20 of 23 subtype-specific compounds had better associations with subtype than with doubling time (mean log ratio of $p$-values = 0.87, standard deviation 1.09). Moreover, 11 of 23 subtype-specific compounds were most effective in the most slowly growing luminal cell lines (Table 1). One agent, 5-fluorouracil, was not significant in the subtype test alone but showed strong significance in the ANCOVA model for both class and doubling time. (Fig. S3B). We conclude that in most cases, the 3-day proliferation assay detects molecular signature-specific responses that are not strongly influenced by growth rate.

To assess the effects of cell line subtype and growth rate on drug sensitivity, we performed a set of 2-way analysis of covariance (ANCOVA) tests, one for each of the three cell line classification schemes: i) luminal vs. basal vs. claudin-low; ii) luminal vs. basal + claudin-low; and iii) ERBB2AMP vs. non-ERBB2AMP. This yielded 6 sets of $p$-values (2 main effects x 3 classification schemes); we separately adjusted the two sets of main effect $p$-values for multiple comparisons. We used the R functions lm and Anova (available as part of the car package).

Integrated Pathway Analysis
Integration of copy number, gene expression and pathway interaction data was performed using the PARADIGM software(1). Briefly, this procedure infers integrated pathway levels (IPLs) for genes, complexes, and processes using pathway interactions and genomic and functional genomic data from a single cell line or patient sample. TCGA breast cancer data was obtained from the TCGA DCC on November 7, 2010. TCGA and cell line gene expression data were median probe centered within each data set separately. All of the values in each of these datasets (either the cell lines or TCGA tumor samples) were rank transformed and converted to –log10 rank ratios before supplying to PARADIGM. Pathways were obtained in BioPax Level 2 format on October 13, 2010 from http://pid.nci.nih.gov/ and included NCI-PID, Reactome, and BioCarta databases. Interactions were combined into a merged Superimposed Pathway (SuperPathway). Genes, complexes, and abstract processes (e.g. “cell cycle”) were retained as pathway concepts. Before merging gene concepts, all gene identifiers were translated into HUGO nomenclature. All interactions were included and no attempt was made to resolve conflicting influences. A breadth-first undirected traversal starting from P53 (the most
connected component) was performed to build one single component. The resulting merged pathway structure contained a total of 8768 concepts representing 3491 proteins, 4757 complexes, and 520 processes. Expectation-Maximization parameters for PARADIGM were trained on the cell line data and then applied to the TCGA samples. Data from the cell lines and tumor samples were then combined into a single data matrix. Any entry without at least 1 value above 0.5 IPL in either the data from cell lines or tumor samples was removed from further analysis.

**TCGA and cell line clustering**

Using PARADIGM IPLs, cell lines were clustered together with TCGA tumor samples to determine if cell lines were similar to tumor samples of the same subtype. Well-studied areas of the SuperPathway contain genes with many interactions (hubs) and large signaling chains of many intermediate complexes and abstract processes for which no direct data is available. To avoid bias toward due to the presence of hubs, pathway concepts with highly correlated vectors (Pearson correlation coefficient > 0.9) across both the cell line and tumor samples were unified into a single vector prior to clustering. This unification resulted in 2351 non-redundant vectors from the original 8768 pathway concepts.

Samples were clustered using the resulting set of non-redundant concepts. The matrix of inferred pathway activities for the 46 breast cancer cell lines and 183 TCGA tumor samples was clustered using complete linkage hierarchical agglomerative clustering implemented in the Eisen Cluster software package version 3.0. Uncentered Pearson correlation was used as the metric for the pathway concepts and Euclidean distance was used for sample metric (Fig. S4).

To quantify the degree to which cell lines clustered with tumor samples of the same subtype, we compared two distributions of t-statistics derived from Pearson correlations (Fig. S5). Let $C_s$ be the set of cell lines of subtype $s$. Similarly, let $T_s$ be the set of TCGA tumor samples of subtype $s$. For example, $C_{basal}$ and $T_{basal}$ are the set of all basal cell lines and basal tumor samples respectively. The first distribution was made up of t-statistics derived from the Pearson correlations between every possible pair containing a cell line and tumor sample of the same subtype; i.e. for all subtypes $s$, every pairwise correlation t-statistic was computed between a pair $(c, t)$ such that $c \in C_s$ and $t \in T_s$. The second distribution was made of correlation t-statistics between samples of different subtypes again from the same origin. We performed a Kolmogorov-Smirnov test to compare the distributions. We repeated this analysis using samples from the same source (cell line or tumor) to verify that cells of the same subtype have overall pathway activities that are more similar than cells of different subtypes. As above, the first distribution was made up of t-statistics between pairs of samples of the same subtype and the same origin (cell line or tumor). The second distribution was made of correlation t-statistics between samples of different subtypes again from the same origin.

We assessed the significance of the subpathways by comparing to subnetworks generated from a background model. Specifically, we measured how likely it would be to find the
identified subnetworks with the observed sizes by chance. To this end, we constructed a background set of subnetworks computed from 1000 simulations in which samples were randomly partitioned into two equal bins, which simulated groupings of cancer cell lines reflecting no biological relevance. Statistical Analysis of Microarrays (SAM) then was used to compute differential pathway activity scores for each concept and each random partitioning using the same thresholds as with the original subtype definitions. Histograms of the subpathway sizes obtained from the random partitions were compared against the subpathway sizes derived from the original subtypes to gauge significance. Our analysis shows that subnetworks derived from the original basal, luminal, claudin-low, and ERBB2 AMP definitions are significantly larger than those subnetworks obtained from random partitionings. This is true for both the size of the entire subpathway (total number of nodes in the graph) as well as for the largest connected component. Histograms and empirical Z-scores were collected from this random partitioning analysis (see Fig. S6).

Supplementary Figure and Table Legends

Figure S1. Genomic and transcriptional profiles of the breast cancer cell lines. A. Hierarchical consensus clustering matrix for 55 breast cancer cell lines showing 3 clusters (claudin-low, luminal, basal) based on gene expression signatures. For each cell line combination, color intensity is proportional to consensus. B. DNA copy number aberrations for 43 breast cancer cell lines are plotted with log_{10}(FDR) of GISTIC analysis on the y-axis and chromosome position on the x-axis. Copy number gains are shown in red with positive log_{10}(FDR) and losses are shown in green with negative log_{10}(FDR).

Figure S2. GI50 calculations are highly reproducible. A. Each bar represents a count of the frequency of replicated drug/cell line combinations. Most cell lines were tested only one time against a particular compound, but some drug/cell line combinations were tested multiple times. B. Each boxplot represents the distribution of median absolute deviations for drug/cell line pairs with 3 or 4 replicates. C. Example drug response curves for HCC1395 treated with cisplatin. Data from three experiments are shown, each plotted in a unique color. Each dot represents the growth inhibition following three days of treatment with one of 10 concentrations of cisplatin. For each dose of each experiment, measurements are performed in triplicate. The x-axis represents increasing cisplatin concentration; the y-axis indicates growth inhibition following treatment. A single curve is fit to the set of 30 data points (3 untreated and 27 treated). The vertical line represents GI50, which is extrapolated from the fitted curve. Across multiple experimental replicates, the dose-response curve is highly reproducible. D, E, F. Example drug response curves for three other cell lines, each treated with a different compound. Convention as in C.

Figure S3. Doubling time varies across cell line subtype. A. Growth rate, computed as the median doubling time in hours, of the breast cancer cell lines subtypes are shown as box-plots. The basal and claudin-low subtypes have shorter median doubling time as
compared to luminal and ERBB2^{AMP} subtypes, Kruskal-Wallis $p$ value ($p = 0.006$). B. The ANCOVA model shows strong effects of both subtype and growth rate on response to 5-FU. Luminal (black) and basal/claudin-low (red) breast cancer lines each show significant associations to growth rate but have distinct slopes.

**Figure S4. Heatmap of non-redundant PARADIGM activities for both cell line and TCGA samples.** Cluster dendrogram represents Euclidian distance between samples and was created using Eisen Cluster and drawn using Java Treeview. Each row represents a network feature, each column represents a sample (tumor or cell line). Colored bars below dendrogram indicate sample subtype (upper) and sample cohort (lower). Overall, cell lines and tumors are intermixed, and subtypes tend to cluster together, indicating that the tumors and cell lines share many of the same network features.

**Figure S5. Inferred pathway activities are more strongly correlated within subtypes than within cohorts.** A. Histogram of t-statistics derived from Pearson correlations computed between cell lines and TCGA samples of the same subtype (red) compared to t-statistics of Pearson correlations between cell lines of different subtypes (black). X-axis corresponds to the Pearson correlation t-statistic; y-axis shows the density of (cell-line, cell-line) or (cell-line, TCGA sample) pairs. K-S test ($p < 1 \times 10^{-22}$) indicates cell lines and TCGA samples of the same subtype are more alike than cell lines of other subtypes. B. Pairwise Pearson correlations of cell line samples within the same subgroup (red) versus cell line samples in different subgroups (black). C. Pairwise correlations of TCGA breast cancer samples within the same subgroup (red) versus cell line samples in different subgroups (black).

**Figure S6. The cell line networks are highly significant.** The significance of the subpathways identified by our method was assessed by comparing the size of our subpathways to the size of the subpathways generated from a background model in which cells were randomly partitioned into groups, rather than in the original subtype definitions. The subpathway sizes were measured in two ways, the total number of nodes in the subpathway (A,C,E,G) and the number of nodes in the largest connected component of the subpathway (B,D,F,H). The luminal (A,B), ERBB2^{AMP} (C,D), claudin-low (E,F), and basal (G,H) subpathway sizes are shown as red dotted lines compared against the distribution of null subpathway sizes. In all cases the subpathway sizes for the true subtype partitioning are significantly larger than the subpathway sizes for the background model.

**Dataset S1.** Transcriptional, genomic and phenotypic characteristics of cell lines in the panel.

**Dataset S2.** Drug response data for each cell line tested against 77 therapeutic compounds. Data are -log10 transformed. These data were used to determine subtype specific responses.

**Dataset S3.** Pearson correlations between drug responses for all compound pairs.
Dataset S4. Subtype associations for all therapeutic compounds. Both raw $p$-values and FDR-corrected $q$-values are shown.

Dataset S5. Censored drug response data. GI50 values that are same as maximum experimental concentration used for different drugs were removed. Data are $-\log_{10}$ transformed. These data were used to identify responses associated with copy number aberrations.

Dataset S6. Non-redundant PARADIGM activities for cell lines and TCGA samples share similar subtype enrichment. Non-redundant pathway entities are along the rows, with subtype-specific SAM scores along the columns, for cell lines alone, TCGA samples alone, and the combined cell line and tumor samples (“BOTH”) as shown in Figure S4. Each SAM score has been ranked within the source-specific subtype and average ranks were computed between the cell lines and TCGA samples for the same subtype (luminal, basal, claudin-low and ERBB2$^{AMF}$).

Dataset S7. Subtypes for TCGA breast tumor samples, as determined by the TCGA AWG using hierarchical clustering of an intrinsic gene list. Data were obtained from the TCGA on November 6, 2010.

Waterfall plots
Waterfall plots of breast cancer subtypes and anti-cancer compounds follow after the supplementary figures. Association of clinical subtypes of breast cancer cell lines with 74 anti-cancer compounds. Each bar represents response sensitivity for one cell line, cell lines are ordered by sensitivity ($-\log_{10}(\text{GI}_{50})$) and colored to indicate subtype.

PARADIGM Network files
Cytoscape files for the PARADIGM breast cancer cell line networks are available at: http://users.soe.ucsc.edu/~jstuart/heiser2011/

References

Figure S1

A

B
Figure S2

A

Number of replicates

Count

0 100 200 300 400 500 600 700
1 2 3 4 5 6

B

Median Absolute Deviation (MAD)

3 4

C

HCC1395 : Cisplatin

Growth Inhibition

0
0.0 0.2 0.4 0.6 0.8 1.0 1.2

Cisplatin concentration (M)

0 3.2e-9 8.0e-8 2.0e-6 5.0e-5

D

HCC1954 : GSK1070916

Growth Inhibition

0
0.0 0.2 0.4 0.6 0.8 1.0 1.2

GSK1070916 concentration (M)

0 4.3e-10 1.1e-8 2.7e-7 6.7e-6

E

HCC1806 : Gefitinib

Growth Inhibition

0
0.0 0.2 0.4 0.6 0.8 1.0 1.2

Gefitinib concentration (M)

0 4.3e-10 1.1e-8 2.7e-7 6.7e-6

F

MDAMB231 : Paclitaxel

Growth Inhibition

0
0.0 0.2 0.4 0.6 0.8 1.0 1.2

Paclitaxel concentration (M)

0 4.3e-10 1.1e-8 2.7e-7 6.7e-6
Figure S3

A

B
Figure S4
Figure S5

A

TCGA-Cell line subtype correlations

B

Cell line subtype correlations

C

TCGA subtype correlations

- Pearson Correlation T-statistic

[Graphs showing correlation density for TCGA and cell line subtype correlations, with red and black lines representing different subtypes]
-log10 GI50 (M)
5-FU (pyrimidine analog, thymidylate synthase)
AG1478 (EGFR)

-\log_{10} GI50 (M)

Luminal
ERBB2AMP
Basal
Claudin-low
AS-252424 (PI3K gamma)

-\log_{10} GI50 (M)

Basal
ERBB2AMP
Luminal
Claudin-low
BEZ235 (PI3K)

-\log_{10} GI50 (M)

Claudin–low
ERBB2AMP
Luminal
Basal
BIBW 2992 (EGFR and HER2 inhibitor)

-log10 GI50 (M)

- ERBB2AMP
- Luminal
- Basal
- Claudin−low
Bortezomib (Proteasome, NFkB)

-\log_{10} GI50 (M)

Luminal
Basal
ERBB2AMP
Claudin–low

UACC893
HCC70
HCC1187
HCC1419
HCC2185
AU565
SUM152PE
SUM185PE
MDAMB157
MDAMB453
HCC1395
HCC1937
HCC202
HCC2185
HCC2474
SUM149PT
SUM159PT
HCC1937
SKBR3
T47D
MDAMB134VI
MDAMB143
MDAMB436
MDAMB199
HCC1353
SUM225CWN
HCC38
SUM1315MO2
MDAMB468
CAMA1
ZR751
MCY7
MDM408
BT483
BT474
UACC812
MDAMB231
MDAMB415
HCC1428
SUM169PT
MDAMB361
LY2

The graph shows the sensitivity of various cell lines to Bortezomib, measured as -\log_{10} GI50 (M). The sensitivity is color-coded by different types of breast cancer: Luminal, Basal, ERBB2AMP, and Claudin–low.
Bosutinib (Src)

−log10 GI50 (M)

-ERBB2AMP
- Basal
- Claudin–low
- Luminal
Carboplatin (DNA cross–linker)

-\log_{10} GI50 (M)

Luminal
Claudin–low
ERBB2AMP
Basal
Doxorubicin (Topoisomerase II)

-\log_{10} GI50 (M)

- Luminal
- Claudin-low
- ERBB2AMP
- Basal

Legend:
- Luminal
- Claudin-low
- ERBB2AMP
- Basal

Data for various cell lines:
- HCC2185
- HCC38
- UACC812
- AU565
- SUM52PE
- ZR7530
- SKBR3
- HCC1187
- ZR751
- BT483
- HCC1806
- HCC1954
- LY2
- SUM1315MO2
- MDAMB453
- MDAMB231
- ZR75B
- HCC1395
- CAMA1
- 600MPE
- BT474
- SUM185PE
- SUM159PT
- HCC3153
- MDAMB415
- MDAMB157
- MCF7
- HCC1419
- HCC1143
- HCC202
- MDAMB436
- MDAMB175VI
- MDAMB468
- UACC893
- HCC1428
- HCC134VI
- HCC70
Epirubicin (Topoisomerase II)

-\log_{10} GI50 (M)

Claudin–low
Luminal
ERBB2AMP
Basal

SUM1315MO2
HCC38
MDAMB159PT
HCC1954
BT483
HCC1937
LY2
SUM149PT
MDAMB453
MDAMB361
MDAMB157
MDAMB468
MDAMB436
UACC893
HCC1187
MDAMB134VI
BT474
Gemcitabine (pyrimidine analog metabolite)

-\log_{10} GI50 (M)

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Basal</th>
<th>ERBB2AMP</th>
<th>Claudin−low</th>
<th>Luminal</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC1806</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BT549</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC38</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUM52PE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDAMB175VII</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BT483</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDAMB231</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUM159PT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SKBR3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC1143</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC1149PT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDAMB453</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUM149PT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AU565</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC2185</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZR751</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LY2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDAMB436</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZR75B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDAMB468</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC3153</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAMA1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC1187</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC415</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUM185PE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC1356</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC1395</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC1937</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T47D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDAMB445</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC202</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC1428</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCF7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC70</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BT474</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC1419</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UACC893</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC1964</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Glycyl–H–1152 (Rho kinase)

- log10 GI50 (M)

HCC70
HCC1187
HCC38
MDAMB134VI
SUM159PT
MDAMB468
HCC2185
ZR751
BT20
AU565
CAMA1
SUM52PE
SUM1315MO2
T47D
HCC1143
HCC1419
MCF7
MDAMB231
MDAMB453
SUM149PT
HCC3153
MDAMB361
MDAMB175VII
HCC1954
MDAMB415
UACC812
MDAMB436
BT483
SKBR3
HCC1428
BT474
HCC1997
ZR75B

Basal
Claudin–low
Luminal
ERBB2AMP
-log10 GI50 (M)
Ibandronate sodium salt (farnesyl diphosphate synthase)

- log10 GI50 (M)

Claudin−low
ERBB2AMP
Luminal
Basal

HCC1395
HCC1419
HCC2185
BT20
HCC1806
MDAMB175VII
T47D
SUM52PE
HCC1937
SUM159PT
HCC1143
MDAMB415
SUM1315MO2
HCC38
MDMB134VI
HCC70
HCC1954
HC38
HCC483
MDMB231
ZR751
SKBR3
MDMB468
BT474
MDMB453
HCC70
MDMB231
HCC3153
UACC812
CAMA1
HCC1187
SUM149PT
AU565
SUM225CWN
ICRF-193 (PLK1, topo II)

-\log_{10} GI50 (M)

- Luminal
- Claudin-low
- ERBB2AMP
- Basal

Gene List:
- ZR75B
- HCC38
- SUM159PT
- AU565
- ZR751
- HCC1187
- HCC2185
- SUM52PE
- SKBR3
- MDAMB468
- HCC1954
- SUM149PT
- UACC812
- HCC3153
- MDAMB361
- MDAMB175VII
- HCC70
- MCF7
- LY2
- T47D
- MDAMB415
- MDAMB453
- MDAMB134VI
- HCC1428
- BT20
- MDAMB436
- BT474
- CAMA1
- HCC1937
- HCC1143
- HCC1806
Ispinesib (Kinesin)

-log10 GI50 (M)

Luminal
ERBB2AMP
Basal
Claudin–low
Ixabepilone (Microtubule )

-\log_{10} GI50 (M)

- Luminal
- Claudin-low
- Basal
- ERBB2AMP
Methotrexate (DHFR)

-\log_{10} GI50 (M)

ERBB2AMP
Claudin–low
Basal
Luminal
MLN4924 (NAE)

-\log_{10} GI50 (M)

Basal
ERBB2AMP
Claudin-low
Luminal
NSC 663284 (cdc25s)
NU6102 (CDK1/CCNB)

-\log_{10} GI50 (M)

4.0 4.5 5.0 5.5 6.0

Luminal
Claudin−low
Basal
ERBB2AMP

SUM185PE
SUM1315MO2
SUM52PE
HCC1395
HCC1187
HCC149PT
HCC38
CAMA1
MDAMB453
SUM159PT
HCC1428
HCC1143
MDAMB468
ZR75B
T47D
HCC2185
HCC3153
MDAMB361
ZR751
HCC70
HCC1806
BT474
HCC1419
BT20
SKBR3
MDMB415
UACC812
MCF7
HCC1954
MDMB134VI
LY2
SUM225CWN
MDMB436
MDMB197VI
HCC1937
MDMB134VI
LY2
BT483
Oxaliplatin (DNA cross-linker)

-log10 GI50 (M)

Basal
ERBB2AMP
Claudin-low
Luminal
Oxamflatin (HDAC)

-log10 GI50 (M)

Claudin–low
ERBB2AMP
Luminal
Basal

HCC38
BT474
MDMB453
SUM185PE
HCC2185
HZR75B
HCC70
HCC1428
HCC1143
CAM41
SUM52PE
AU565
HCC1187
MDAMB134VI
SUM149PE
HCC1806
MDAMB361
BT483
MDMB415
SUM225CWN
T47D
SKBR3
LY2
HCC1419
HCC1897
HCC1937
HCC3153
HCCH1954
MCF7
UACC812
ZR751
SUM1315MO2
MDAMB468
BT20
MDAMB175VII
MDAMB436
Paclitaxel (Microtubule)

-\log_{10} GI50 (M)

- Luminal
- Claudin-low
- ERBB2AMP
- Basal

Sam52PE
MDAMB231
MDAMB4415
MDAMB22502
HCC1954
HCC2185
HCC38
HCC70
HCC1806
HCC3187
UACC812
SUM149PT
MDAMB134VI
BT474
MDAMB453
LY2
CAMA1
SKBR3
UACC893
MDAMB361
SUM159PT
MDAMB175VII
HCC1395
MCF7
HCC1143
MDAMB175VI
HCC3153
ZR7530
SUM185PE
BT483
MDAMB436
600MPE
HCC1419
HCC1428
Pemetrexed (DNA synthesis/repair)

-log10 GI50 (M)

ERBB2AMP
Luminal
Basal
Claudin–low

HCC202
HCC1954
LY2
MDAMB361
MDAMB453
HCC1937
ZR751
HCC1806
SKBR3
CAMA1
MDAMB468
MDAMB134VI
SUM185PE
MDAMB436
MDAMB157
BT474
GZ74
SUM1315MO2
HCC1187
HCC1185
HCC2185
SUM1153
HCC1143
HCC38
BT549
HCC1419
UACC812
HCC70
MCF7
SUM52PE
BT483
HCC1428
AU565
T47D
-log10 GI50 (M)

Rapamycin (mTOR)

- Luminal
- ERBB2AMP
- Basal
- Claudin−low
Sigma AKT1–2 inhibitor (Akt 1/2)

\[-\log_{10} GI50 (M)\]

- Luminal
- ERBB2AMP
- Basal
- Claudin–low

Bar chart showing the sensitivity of various breast cancer cell lines to a Sigma AKT1–2 inhibitor.
TCS 2312 dihydrochloride (chk1)

-\log_{10} GI50 (M)

Claudin–low
Luminal
Basal
ERBB2AMP

HCC1395
HCC38
SUM185PE
LY2
AU565
HCC70
HCC1937
SUM1315MO2
HCC1143
MDAMB415
HCC3153
MDAMB361
SKBR3
CAMA1
600MPE
BT474
BT483
HCC1806
SUM225CWN
HCC1428
MDAMB468
ZR751
MDAMB134VI
MDAMB175VII
BT20
HCC1954
Temsriolimus (mTOR)

-\log_{10} GI50 (M)

- Luminal
- ERBB2AMP
- Claudin-low
- Basal
Topotecan (Topoisomerase I)

-log10 GI50 (M)

Claudin–low
Luminal
ERBB2AMP
Basal

Cell lines: HCC38, SUM1315MO2, SKBR3, HCC1395, BT483, AU565, HCC1806, MDAMB436, ZR751, HCC2185, MDAMB448, UACC812, ZR75B, SUM185PE, MDAMB453, MDAMB134VI, MDAMB415, HCC1143, HCC1153, MDAMB314VI, HDCC3153, HCC1143, HCC1153, LY2, HCC1964, HCC1187, HCC11988, UACC1419, SUM144PE, CAM1, MDAMB157, HCC1428, HCC1436, HCC202, MDAMB231, MCF7, BT474, MDAMB175VII, HTC70.
Trichostatin A (Histone deacetylase)

-\log_{10} GI50 (M)

- ERBB2AMP
- Luminal
- Basal
- Claudin-low
Triciribine (AKT, ZNF217 amplification)

-log\(10\) GI50 (M)

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>ERBB2AMP</th>
<th>Luminal</th>
<th>Basal</th>
<th>Claudin–low</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC202</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BT483</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AU565</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC2185</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LY2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SKBR3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BT474</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC1428</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDAMB453</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC70</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T47D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUM135PE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCF7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC1187</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC1806</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC1419</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDAMB468</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UACC936</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUM135MO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERBB2AMP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luminal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Claudin–low</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Symbols: ERBB2AMP, Luminal, Basal, Claudin–low
VX–680 (aurora kinase)

-\log_{10} GI50 (M)

<table>
<thead>
<tr>
<th>Basal</th>
<th>Claudin-low</th>
<th>Luminal</th>
<th>ERBB2AMP</th>
</tr>
</thead>
</table>

- Log10 GI50 values for various breast cancer cell lines treated with VX–680 (aurora kinase). The graph compares the response of different cell lines to the drug, categorized by basal, claudin-low, luminal, and ERBB2AMP types.
XRP44X (Ras–Net (Elk−3))

-log10 GI50 (M)

Luminal
ERBB2AMP
Basal
Claudin–low

HCC2185
MCF7
AU565
UACC812
MDAMB415
HCC1954
CAM1
HCC1187
MDAMB134VI
MDAMB453
SUM159PT
LY2
SUM52PE
MDAMB361
HCC70
HCC1187
MDAMB468
HCC1806
HCC70
HCC1187
MDAMB48
HCC1806
HCC70
HCC1187
HCC1187
MDAMB36
HCC70
HCC1187
MDAMB175VII
BT474
BT20
T47D
BT483
HCC1937
HCC1419
XRP44X (Ras–Net (Elk−3))
ZM 447439 (AURKA)

-\log_{10} GI50 (M)

Claudin-low
Basal
Luminal
ERBB2AMP

HCC38, HCC1187, MDAMB468, HCC70, HCC2185, AU565, MDAMB361, ZR751, CAMA1, SUM52PE, MDAMB436, HCC1419, BT20, HCC1937, HCC1428, ZR75B, HCC1143, T47D, UACC812, SKBR3, SUM185PE, BT483, MDAMB149PT