# Controversy In Pharmacogenomics

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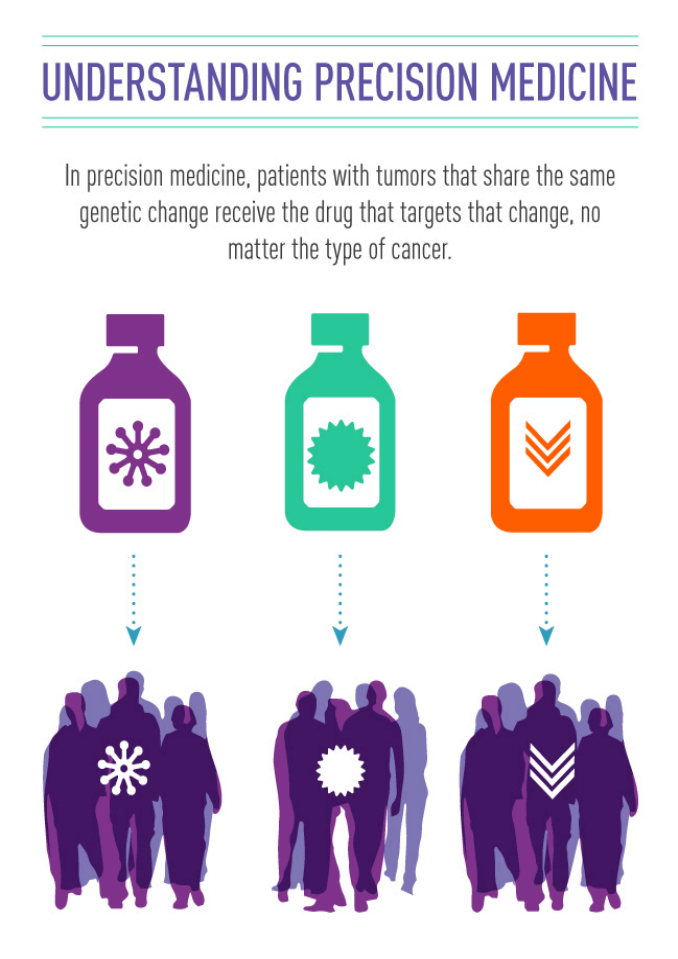
# Outline

- Background and Introduction
- Analysis and Comparison of Results
- Takeaway/Conclusion
- Future Work
- Acknowledgements
- References

*"Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?"*

*- President Obama, January 30, 2015*




# Precision Medicine

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# Great Insight...

LETTER

doi:10.1038/nature11003

## The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity

Jordi Barretina[1,2,3]†*, Giordano Caponigro[4]*, Nicolas Stransky[1]*, Kavitha Venkatesan[4]*, Adam A. Margolin[1]†*, Sungjoon Kim[5], Christopher J. Wilson[4], Joseph Lehár[4], Gregory V. Kryukov[1], Dmitriy Sonkin[4], Anupama Reddy[4], Manway Liu[4], Lauren Murray[1], Michael F. Berger[1]†, John E. Monahan[4], Paula Morais[1], Jodi Meltzer[4], Adam Korejwa[1], Judit Jané-Valbuena[1,2], Felipa A. Mapa[4], Joseph Thibault[5], Eva Bric-Furlong[4], Pichai Raman[4], Aaron Shipway[5], Ingo H. Engels[5], Jill Cheng[6], Guoying K. Yu[6], Jianjun Yu[6], Peter Aspesi Jr[4], Melanie de Silva[4], Kalpana Jagtap[4], Michael D. Jones[4], Li Wang[4], Charles Hatton[3], Emanuele Palescandolo[3], Supriya Gupta[1], Scott Mahan[1], Carrie Sougnez[1], Robert C. Onofrio[1], Ted Liefeld[1], Laura MacConaill[3], Wendy Winckler[1], Michael Reich[1], Nanxin Li[5], Jill P. Mesirov[1], Stac
Barbara L. Weber[4], Jeff Porter[4], Markus Warmutl
Michael P. Morrissey[4]*, William R. Sellers[4]*, Rol

ARTICLE

doi:10.1038/nature11005

## Systematic identification of genomic markers of drug sensitivity in cancer cells

Mathew J. Garnett[1]*, Elena J. Edelman[2]*, Sonja J. Heidorn[1]*, Chris D. Greenman[1]†, Anahita Dastur[2], King Wai Lau[1], Patricia Greninger[2], I. Richard Thompson[1], Xi Luo[2], Jorge Soares[1], Qingsong Liu[3,4], Francesco Iorio[1,5], Didier Surdez[6], Li Chen[2], Randy J. Milano[2], Graham R. Bignell[1], Ah T. Tam[2], Helen Davies[1], Jesse A. Stevenson[2], Syd Barthorpe[1], Stephen R. Lutz[2], Fiona Kogera[1], Karl Lawrence[1], Anne McLaren-Douglas[1], Xeni Mitropoulos[2], Tatiana Mironenko[1], Helen Thi[2], Laura Richardson[1], Wenjun Zhou[3,4], Frances Jewitt[1], Tinghu Zhang[3,4], Patrick O'Brien[1], Jessica L. Boisvert[2], Stacey Price[1], Wooyoung Hur[3,4], Wanjuan Yang[1], Xianming Deng[3,4], Adam Butler[1], Hwan Geun Choi[3,4], Jae Won Chang[3,4], Jose Baselga[2], Ivan Stamenkovic[7], Jeffrey A. Engelman[2], Sreenath V. Sharma[2]†, Olivier Delattre[6], Julio Saez-Rodriguez[5], Nathanael S. Gray[3,4], Jeffrey Settleman[2], P. Andrew Futreal[1], Daniel A. Haber[2,8], Michael R. Stratton[1], Sridhar Ramaswamy[2], Ultan McDermott[1] & Cyril H. Benes[2]

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# … Only one problem

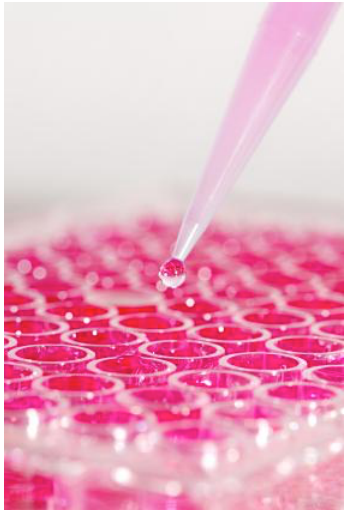
ANALYSIS

doi:10.1038/nature12831

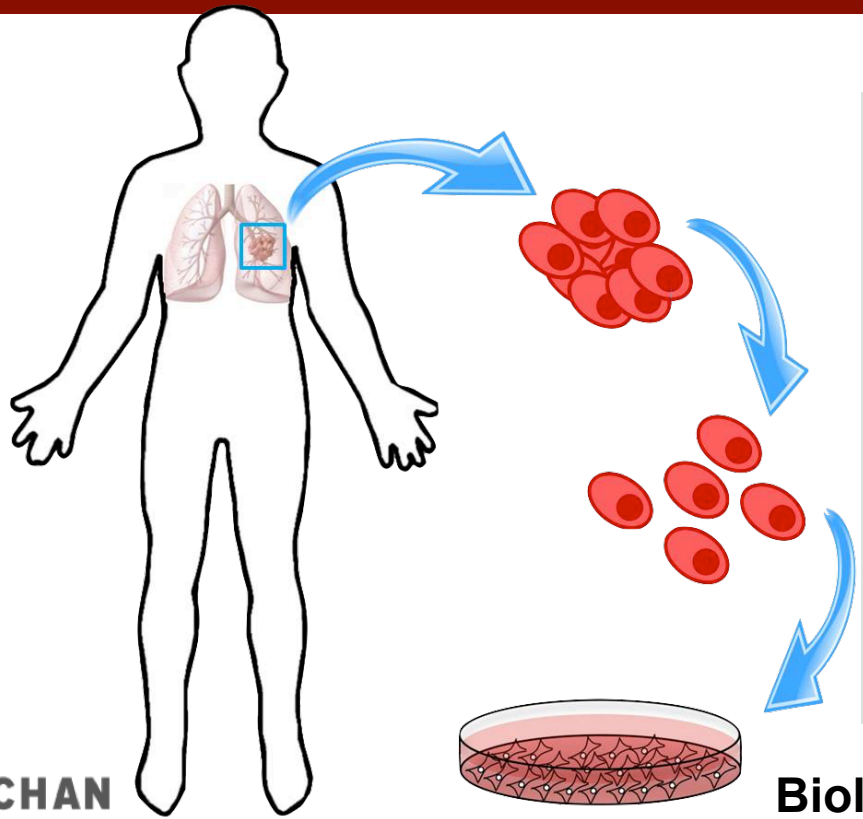
## Inconsistency in large pharmacogenomic studies

Benjamin Haibe-Kains[1,2], Nehme El-Hachem[1], Nicolai Juul Birkbak[3], Andrew C. Jin[4], Andrew H. Beck[4*], Hugo J. W. L. Aerts[5,6,7*] & John Quackenbush[5,8*]

# Obtaining Samples



**Cell Lines**



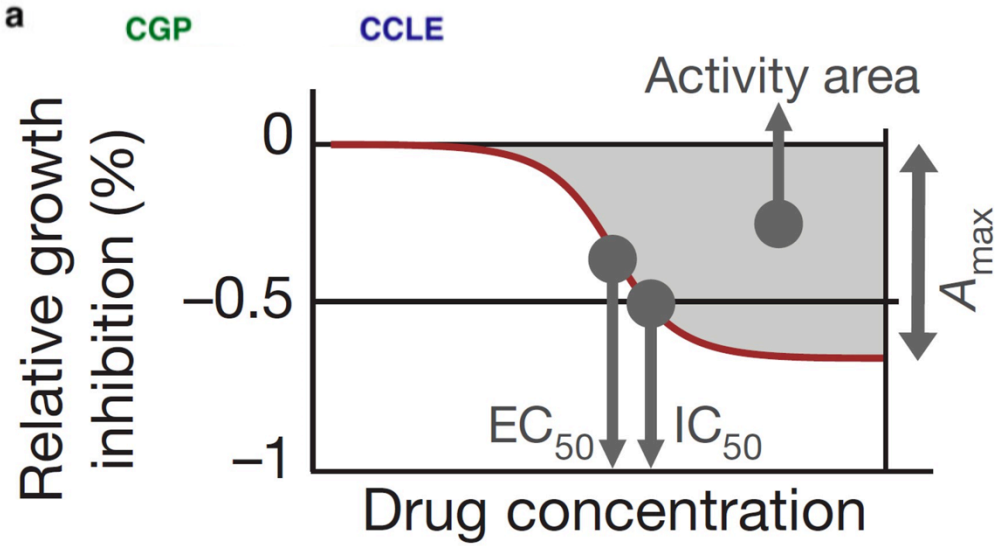
**Biological Replicates**

- Retrieve and genetically transform cell cultures derived from various tissue
- Expose samples to drugs
- Record Drug Response (sensitivity)
- Quantify the effectiveness of the drug (does it work?)

# How They Did It...

- **471 cell lines shared between both data sets for 64 gene mutations**
- **Compared drug sensitivity between CGP and CCLE for 15 drugs**
- **$IC_{50}$: Drug concentration necessary to inhibit 50% of growth**

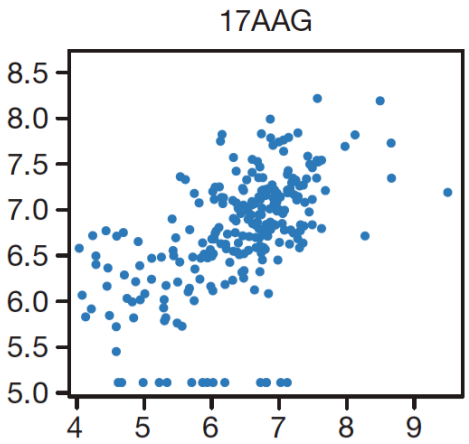
Drugs by Study




Barretina, J. *et al.* (2012) Haibe-Kains et al. (2013)

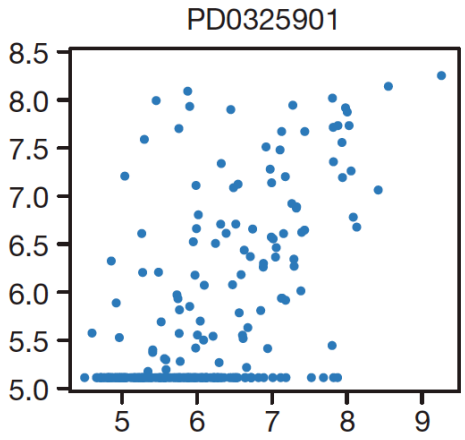
# Close But not Quite...

- Ranked the response of the 471 shared cell lines and computed the Spearman's rank correlations for the $IC_{50}$ values.




moderate correlation r = 0.61

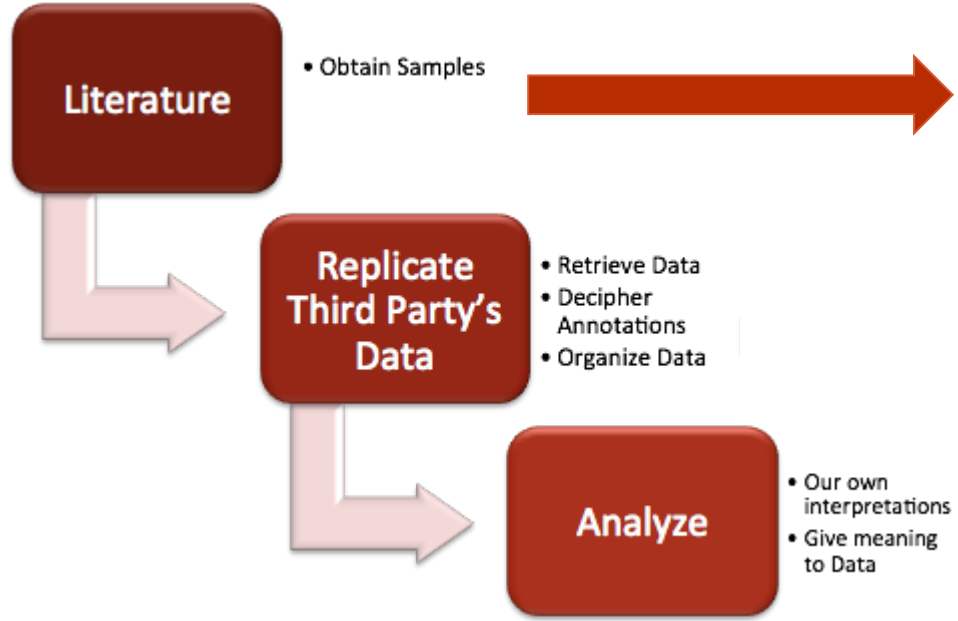
Haibe-Kains, *et al.* (2013).

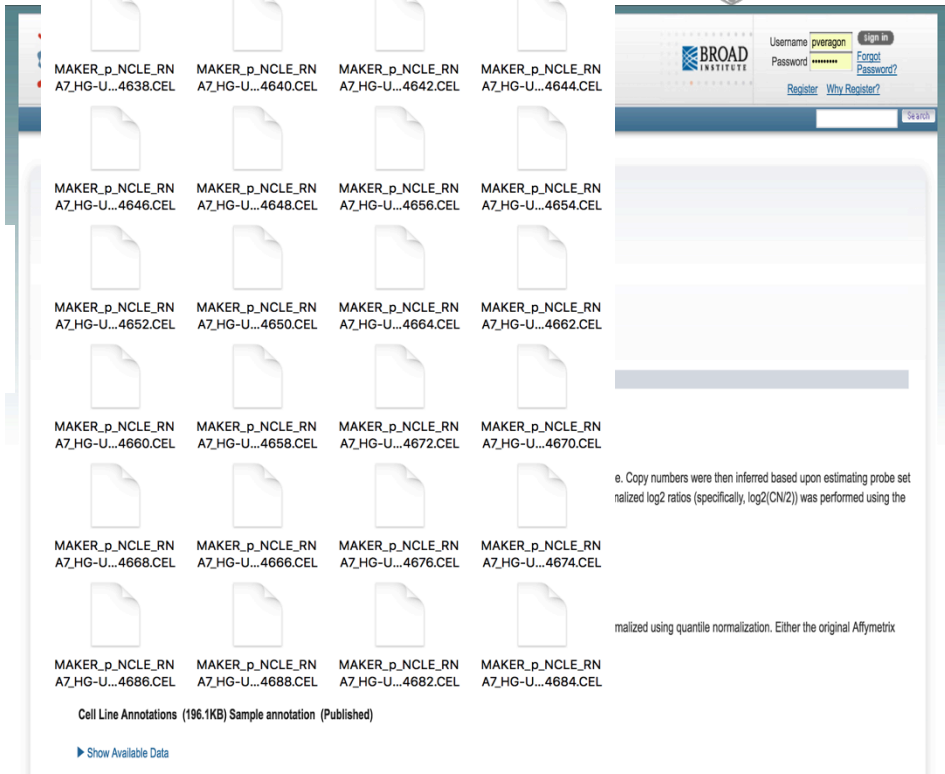



fair correlation r = 0.53

Haibe-Kains, *et al.* (2013).

# Our Interpretation of The Problem

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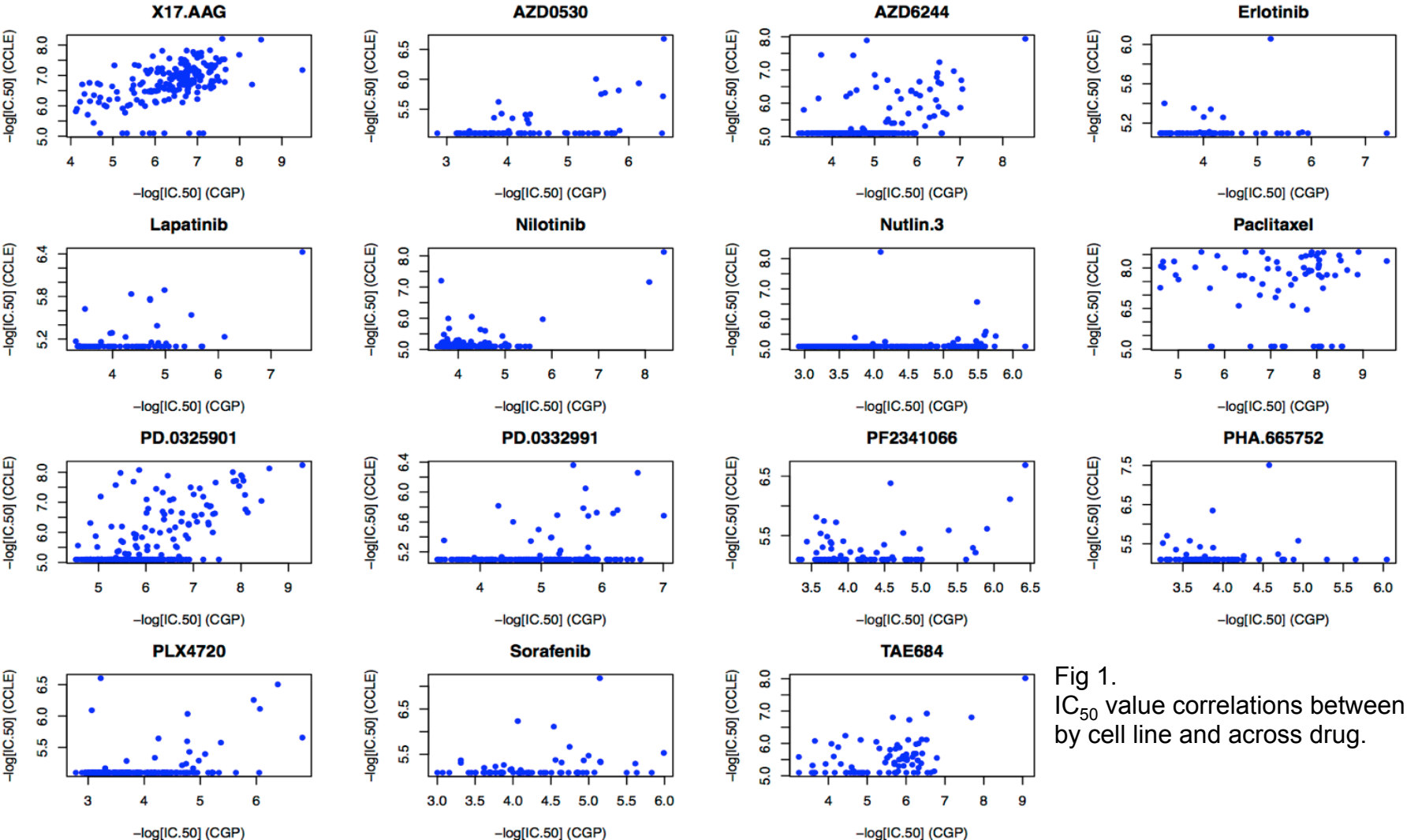



Fig 1.
$IC_{50}$ value correlations between datasets by cell line and across drug.

Haibe-Kains et al. (2013) -- Left
Our results -- Right

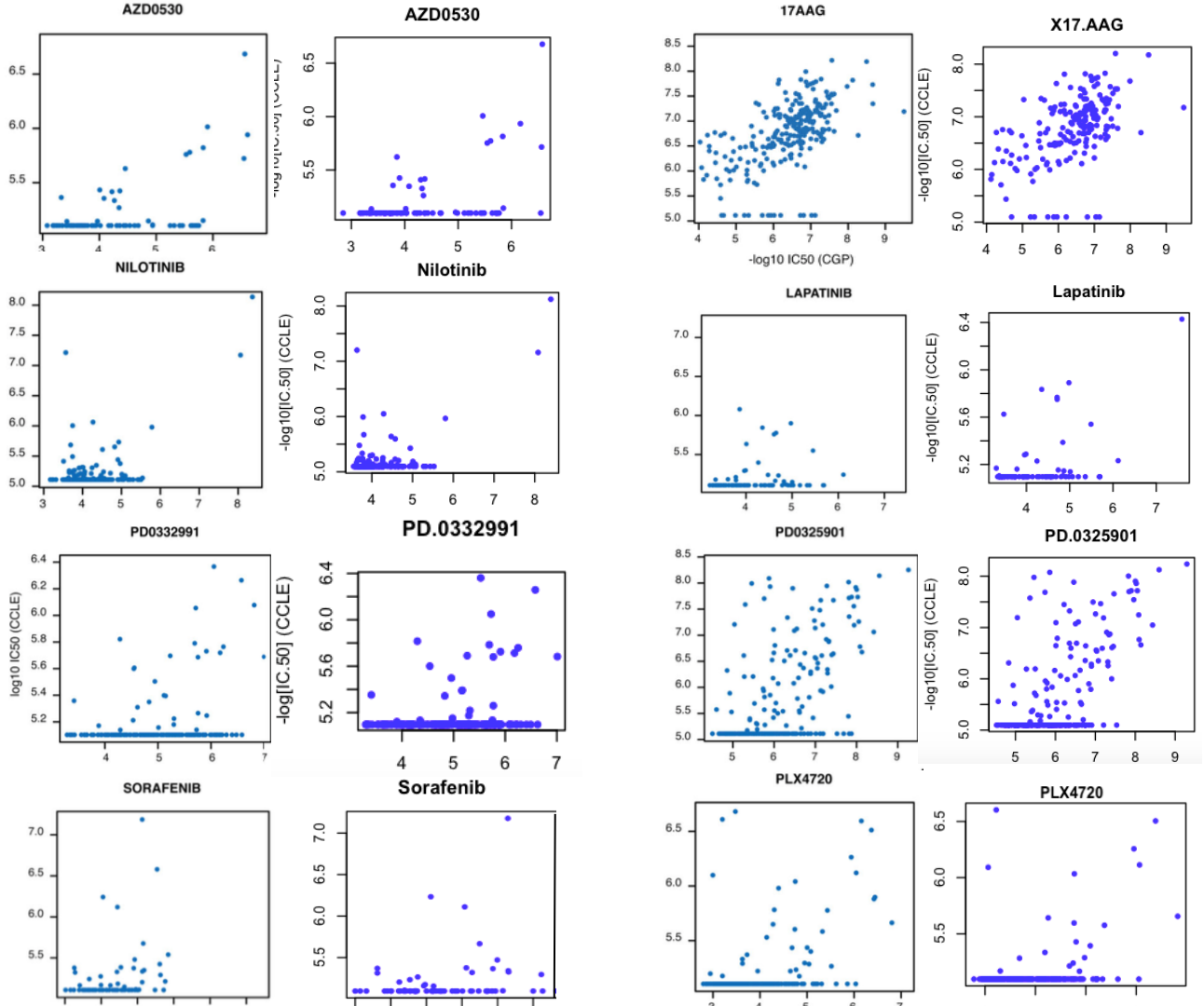
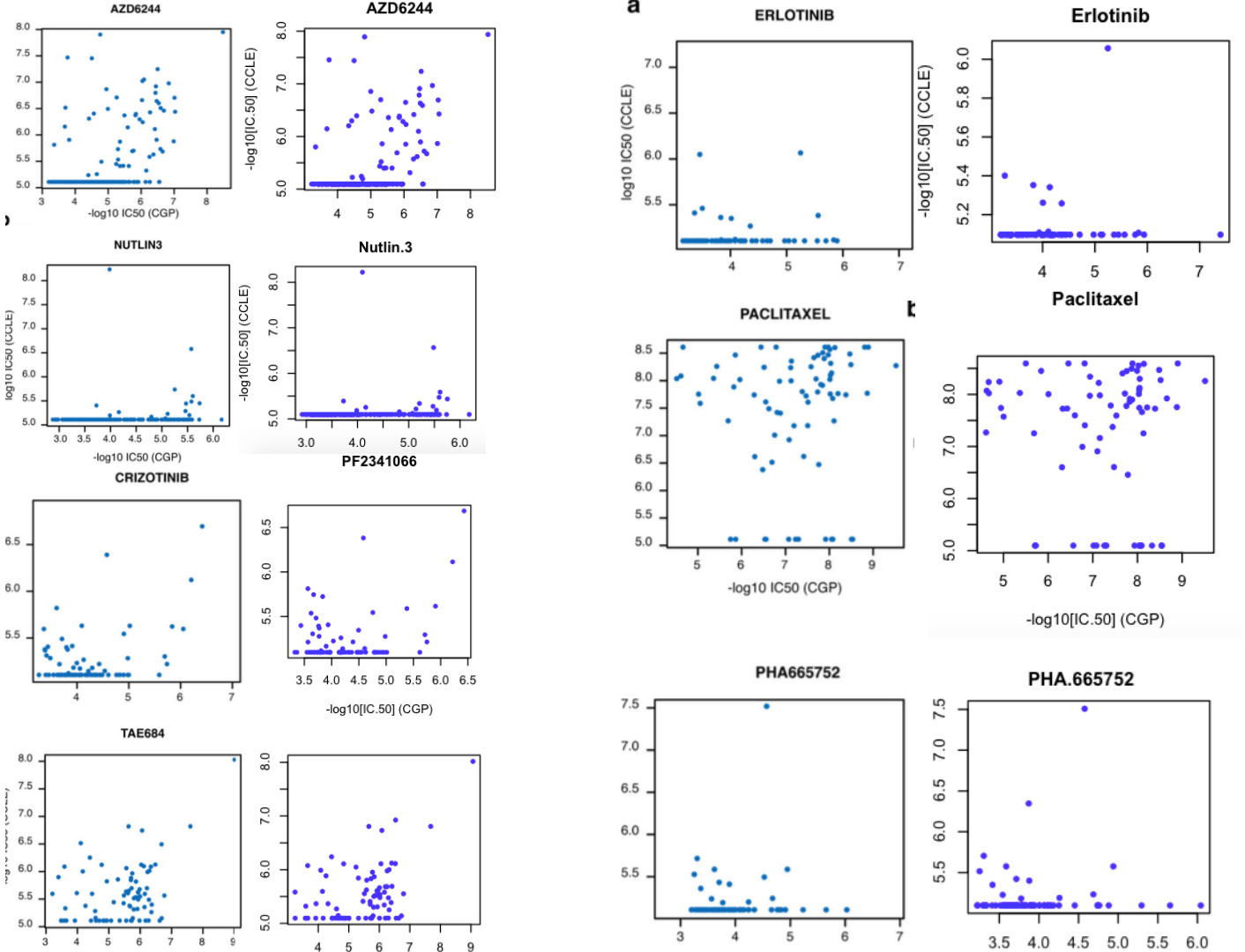



Fig 2.
$IC_{50}$ value comparisons between our analysis and Haibe-Kains et al. (2013).


AZD6244
AZD6244
-log10 IC50 (CGP)
-log10[IC.50] (CCLE)
NUTLIN3
Nutlin.3
log10 IC50 (CCLE)
-log10 IC50 (CGP)
-log10[IC.50] (CCLE)
CRIZOTINIB
PF2341066
-log10[IC.50] (CGP)
TAE684
a
ERLOTINIB
Erlotinib
log10 IC50 (CCLE)
-log10[IC.50] (CCLE)
b
PACLITAXEL
Paclitaxel
-log10 IC50 (CGP)
-log10[IC.50] (CGP)
PHA665752
PHA.665752

# Comparison between Spearman Correlation Coefficients

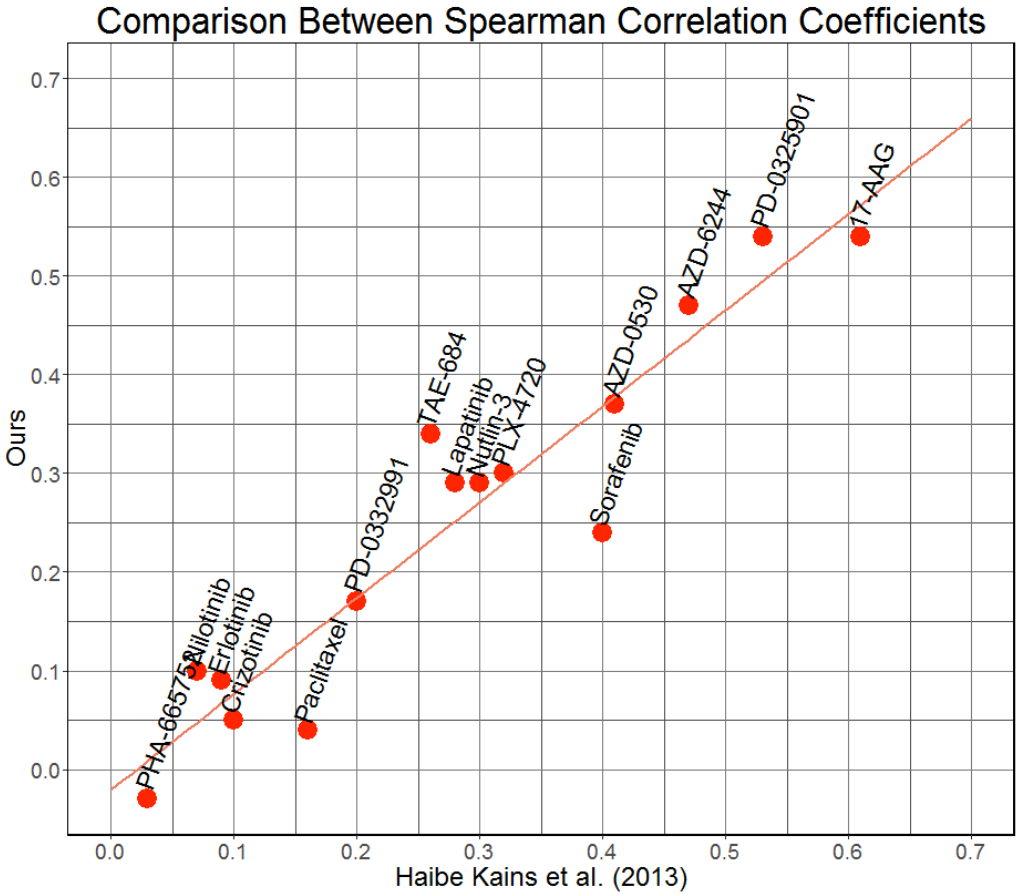
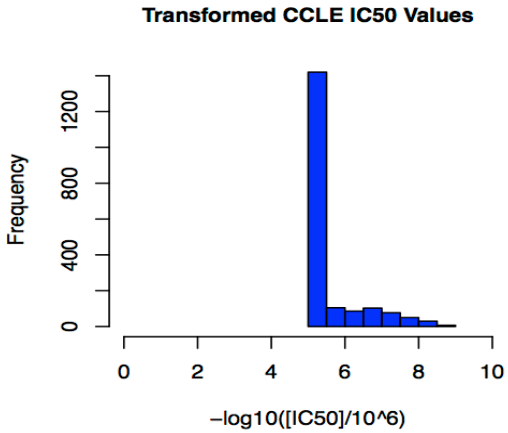



Fig 3. Scatterplot of drug $IC_{50}$ value correlations comparing ours and the literature's.



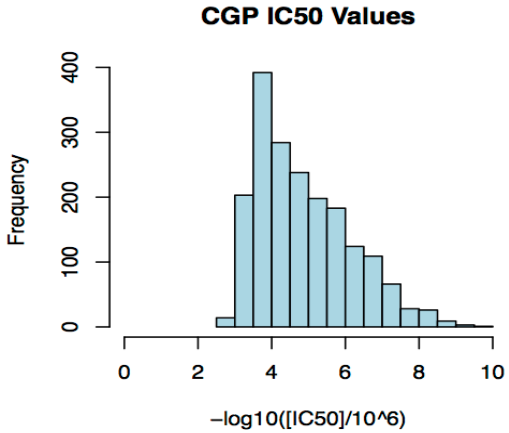
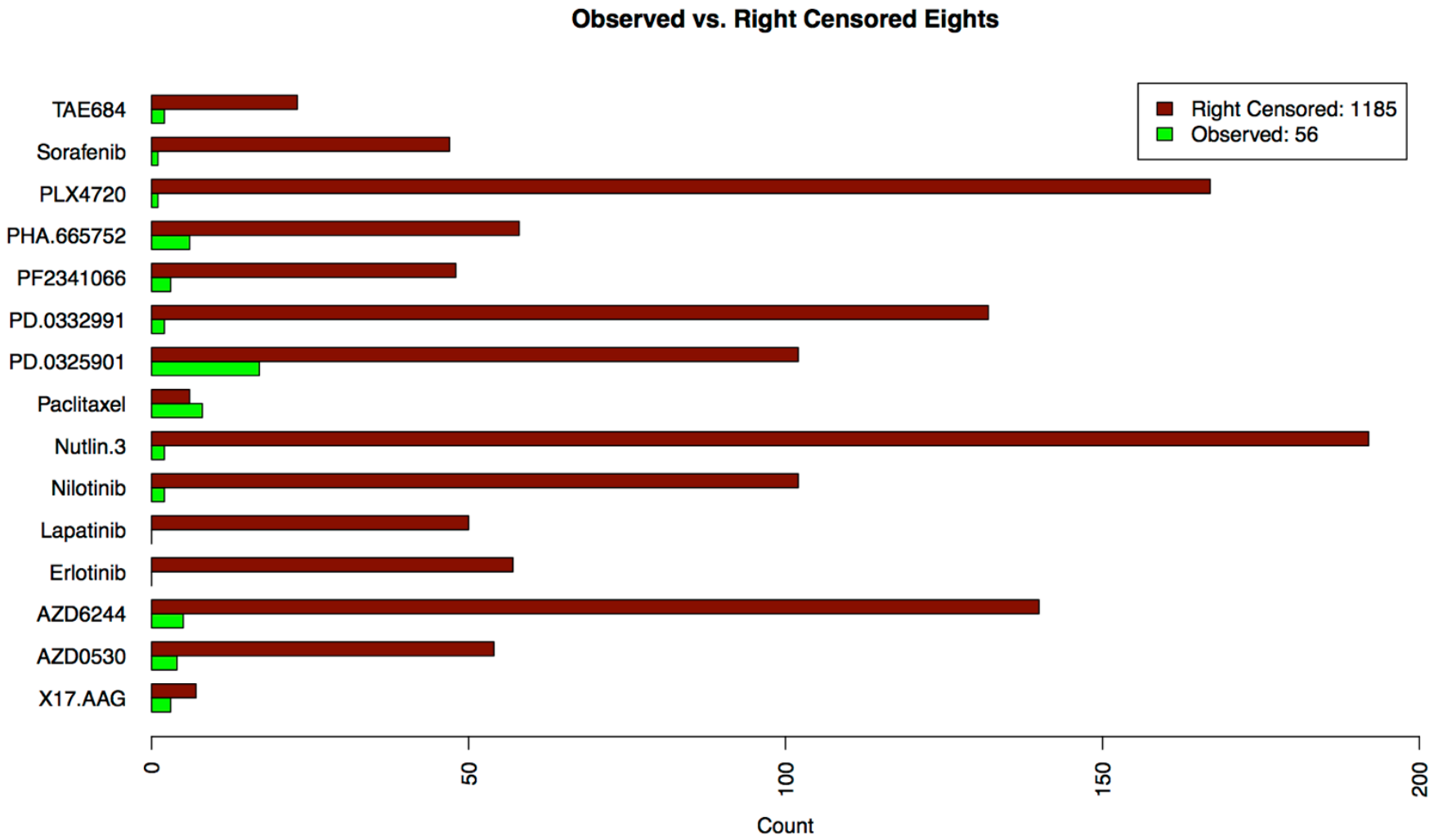




Fig 4.
$IC_{50}$ value distributions by dataset.


Observed vs. Right Censored Eights
Right Censored: 1185
Observed: 56
TAE684
Sorafenib
PLX4720
PHA.665752
PF2341066
PD.0332991
PD.0325901
Paclitaxel
Nutlin.3
Nilotinib
Lapatinib
Erlotinib
AZD6244
AZD0530
X17.AAG
0
50
100
150
200
Count

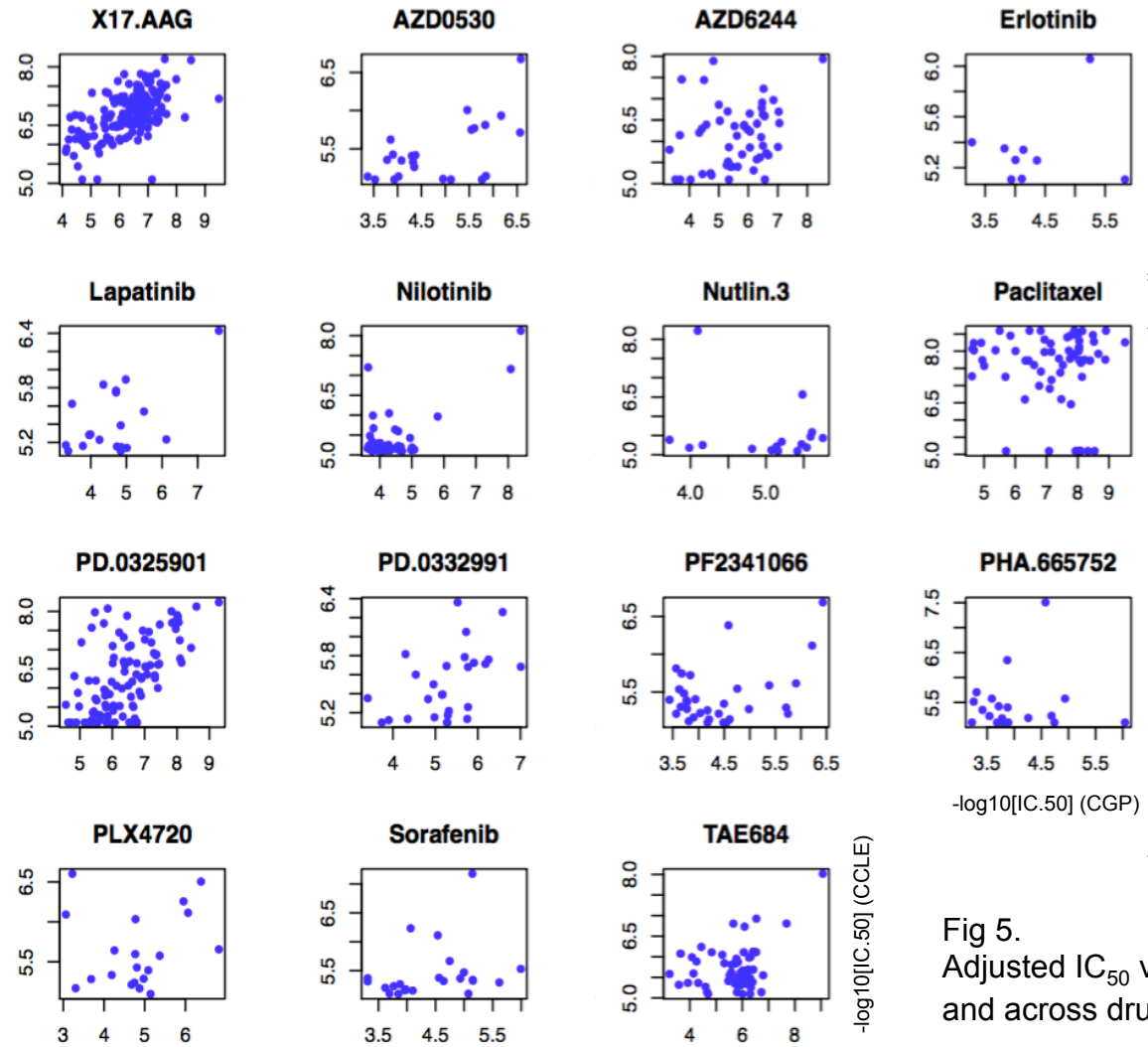



Table 1: Adjusted Correlations

| | Pearson Adjusted | Spearman Adjusted |
|---|---|---|
| X17.AAG | .57 | .55 |
| AZD0530 | .61 | .48 |
| AZD6244 | .26 | .27 |
| Erlotinib | .41 | .03 |
| Lapatinib | .22 | -.28 |
| Nilotinib | .54 | .19 |
| Nutlin.3 | .68 | -.01 |
| Paclitaxel | -.23 | .26 |
| PD.0325901 | -.08 | .02 |
| PD.0332991 | .58 | .55 |
| PF2341066 | .48 | .46 |
| PHA.665752 | .06 | -.10 |
| PLX4720 | .15 | .18 |
| Sorafenib | .27 | .39 |
| TAE684 | .37 | .14 |

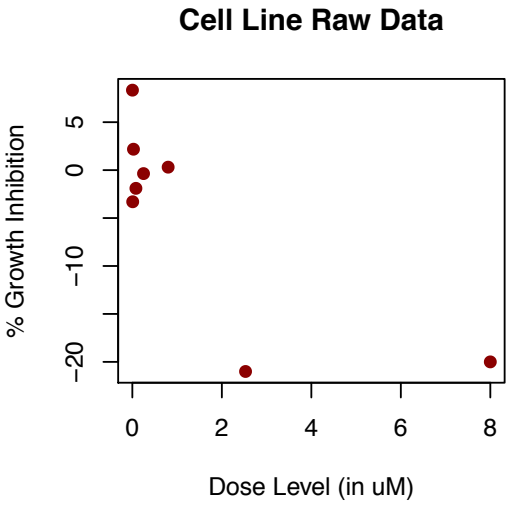
Fig 5.
Adjusted $IC_{50}$ value correlations by cell line and across drug.

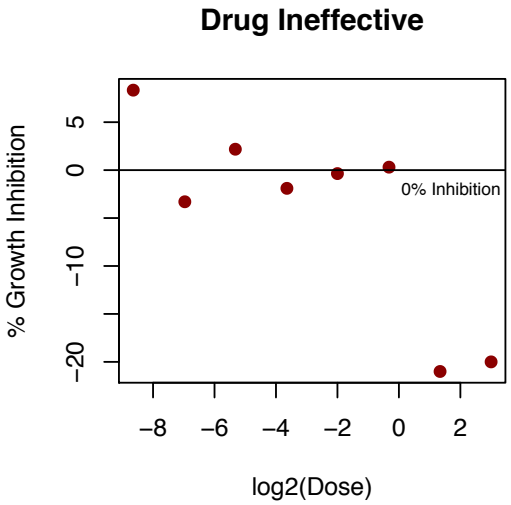
# Correlation table across studies

Table 2: Correlations Across Study and by Drug

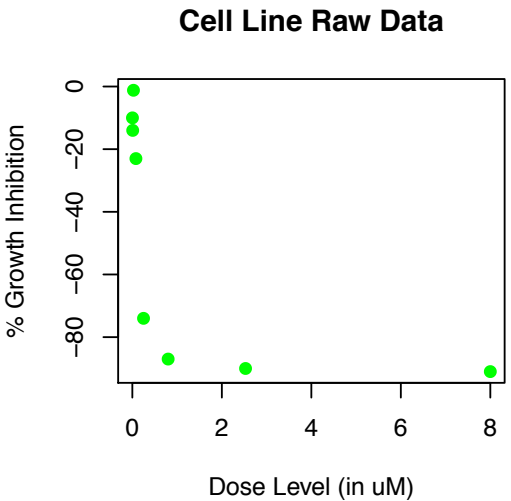
| | Pearson | Pearson Adj | Spearman | Spearman Adj | Spearman Haibe-Kains (2013) |
|---|---|---|---|---|---|
| X17.AAG | .51 | .57 | .54 | .55 | .61 |
| AZD0530 | .48 | .61 | .37 | .48 | .41 |
| AZD6244 | .49 | .26 | .47 | .27 | .47 |
| Erlotinib | .37 | .41 | .05 | .03 | .10 |
| Lapatinib | .11 | .22 | .09 | -.28 | .09 |
| Nilotinib | .48 | .54 | .29 | .19 | .28 |
| Nutlin.3 | .58 | .68 | .10 | -.01 | .07 |
| Paclitaxel | .12 | -.23 | .29 | .26 | .30 |
| PD.0325901 | -.05 | -.08 | .04 | .02 | .16 |
| PD.0332991 | .63 | .58 | .54 | .55 | .53 |
| PF2341066 | .26 | .48 | .17 | .46 | .20 |
| PHA.665752 | .09 | .06 | -.03 | -.10 | .03 |
| PLX4720 | .36 | .15 | .30 | .18 | .32 |
| Sorafenib | .24 | .27 | .24 | .39 | .40 |
| TAE684 | .45 | .37 | .34 | .14 | .26 |

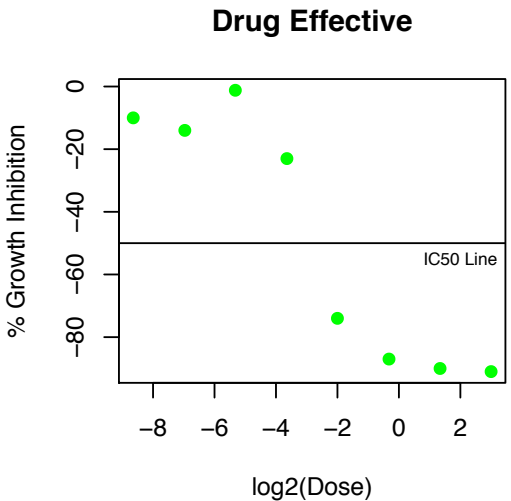
*Adj = Adjusted

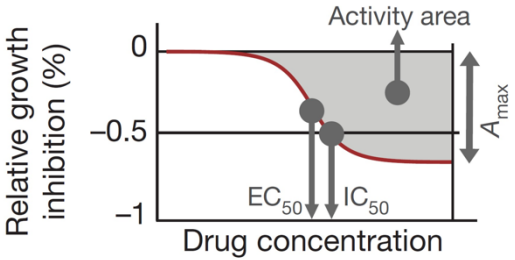



“8”




Barretina, J. *et al.* (2012)

# Takeaway/Conclusion


Genomic features

Biomarkers for specific drugs

Heavy (63%) censorship 1185/1878 Cell Lines

Challenges in pharmacogenomic analyses

# Future Work

Obtain gene expressions of both studies from raw .CEL files

Compare genomic features between studies across all cell lines

Better statistical summary of the curves for drug responses

# Acknowledgments


- Dana-Farber Cancer Institute
- Rafael Irizarry, PhD
- William Townes, MS
- Summer Program in Biostatistics and Computational Biology
- Jessica Boyle, Heather Mattie, Olivia Orta
  Dr. Rebecca Betensky
- Harvard T.H. Chan School of Public Health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# References


Barretina, Caponigro, Stransky et al. The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity. Nature. 2012 Mar 28;483(7391):603-7. doi: 10.1038/nature11003.

Garnett, Mathew J., et al. "Systematic identification of genomic markers of drug sensitivity in cancer cells." *Nature* 483.7391 (2012): 570-575.

Haibe-Kains, Benjamin, et al. "Inconsistency in large pharmacogenomic studies." *Nature* 504.7480 (2013): 389-393.

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# Dichotomization of $IC_{50}$ Values by Drug

Table 3: Dichotomization of $IC_{50}$ Values by Drug

| | Count: ++ | Count: − + | Count: − − | Count:+ − | ($\chi^2_1$, pval) | Fisher (95% CI) |
|---|---|---|---|---|---|---|
| X17.AAG | 65 | 29 | 65 | 29 | (26.0, <.001) | (2.6, 9.8) |
| AZD0530 | 14 | 5 | 34 | 24 | (4.8, <.05) | (1.1, 15.7) |
| AZD6244 | 39 | 8 | 88 | 57 | (25.4, <.001) | (3.1, 19.8) |
| Erlotinib | 14 | 15 | 25 | 26 | (0.0, NS) | (0.3, 2.5) |
| Lapatinib | 6 | 3 | 30 | 27 | (0.5, NS) | (0.4, 14.9) |
| Nilotinib | 13 | 6 | 29 | 21 | (2.9, NS) | (0.9, 11.1) |
| Nutlin.3 | 24 | 19 | 55 | 49 | (0.6, NS) | (0.7, 3.1) |
| Paclitaxel | 13 | 1 | 103 | 91 | (9.3, <.01) | (2.1, 629.4) |
| PD.0325901 | 21 | 15 | 21 | 15 | (1.4, NS) | (0.7, 5.6) |
| PD.0332991 | 62 | 25 | 78 | 41 | (25.8, <.001) | (2.5, 9.0) |
| PF2341066 | 16 | 9 | 71 | 63 | (1.8, NS) | (0.8, 5.5) |
| PHA.665752 | 6 | 7 | 32 | 32 | (0.0, NS) | (0.2, 3.4) |
| PLX4720 | 15 | 4 | 90 | 78 | (6.0, <.05) | (1.3, 18.5) |
| Sorafenib | 13 | 9 | 26 | 22 | (0.6, NS) | (0.6, 5.4) |
| TAE684 | 26 | 14 | 26 | 14 | (6.1, <.05) | (1.3, 9.6) |