

Accelerating pancreatic cancer drug screening by leveraging genomics to select better *in vitro* models

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Background

- The oncology clinical trial success rate is alarmingly low (13.4%)[1] despite urgent unmet clinical needs for new medicines.
- After many decades of major research and funding efforts, pancreatic cancer remains largely intractable with a dismal estimated 5-year survival rate of only 5-6%. [1]
- The projection that pancreatic cancer will be the second leading cause of cancer related death by 2030 [2] compounded by numerous clinical trial failures highlights a growing need for novel approaches to accelerate progress in new medicine development.
- Cell lines are frequently used for pre-clinical compound screening prior to animal models and human testing. Cell line selection criteria typically includes ease of access, robustness and literature prevalence rather than genomic background.
- Others have reported that the genomic derangements in the cell lines most commonly used for *in vitro* cancer studies may not be representative of what is found in cancer patient tumors [3].

Methods

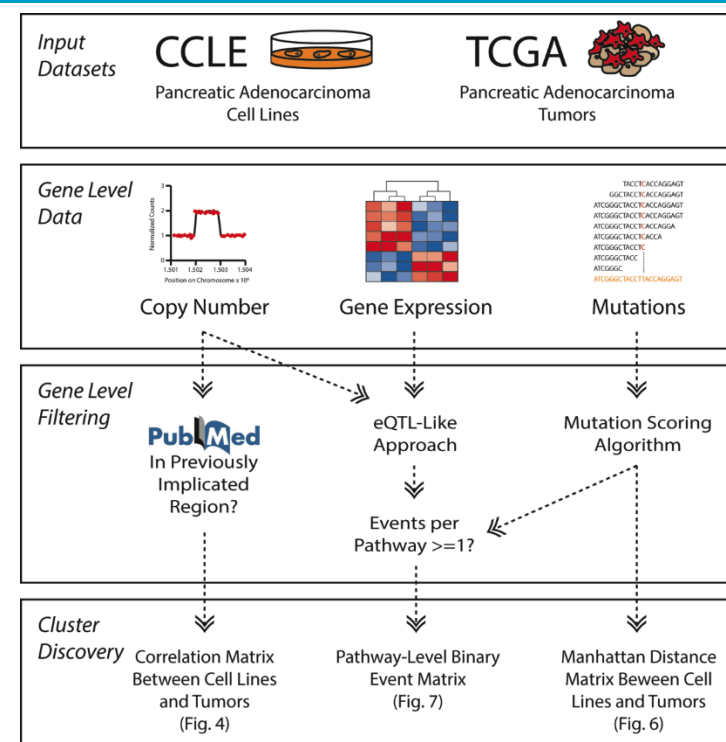


Figure 1. Methodology flowchart. In this study, we leveraged copy number variation (CNV), gene expression, and targeted mutation sequencing or exome data from 91 tumor samples from The Cancer Genome Atlas (TCGA) [4] and 44 cell lines from the Cancer Cell Line Encyclopedia (CCLE) [5] to predict optimal cell lines that mirror pancreatic cancer genomes most closely. CNVs with concurrent gene expression changes were compared to those found in cell lines. Mutations were filtered using various publicly available mutation scoring algorithms. Lastly, similarity between cell lines and mutations were scored using pathway analysis outlined below.

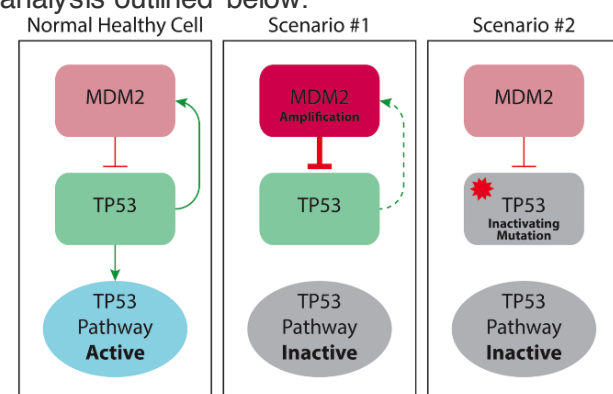


Figure 2. Rationale behind pathway summary methodology. Given that different alterations (CNVs or mutations) within the same pathway can have the same end result, we chose to compare tumors to cell lines based on pathway perturbations in addition to directly comparing mutations and CNVs.

References

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- Domcke, Silvia, et al. "Evaluating cell lines as tumour models by comparison of genomic profiles." *Nature communications* 4 (2013).
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- Barretina, Jordi, et al. "The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity." *Nature* 483. 7391 (2012): 603-607.

Results

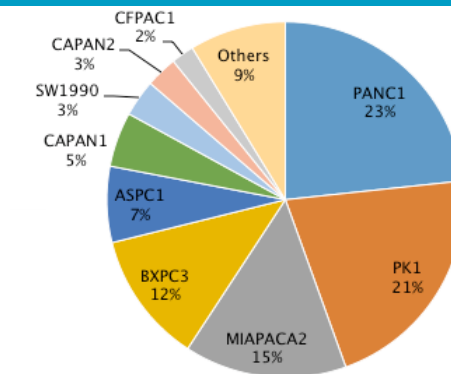


Figure 3. Searching cell line names in PubMed and Google Scholar for all cell lines in CCLE shows a strong bias towards certain cell lines compared to others. PANC1, PK1, MIAPACA2, BXP3, ASPC1, CAPAN1, SW1990, CAPAN2, CFPAC1 account for 91% of the total citations. The remaining 9% includes 35 cell lines: SUIT2, T3M4, HPAC, HPAFII, PSN1, HS766T, QCP1, DANG, KLM1, PL45, KP4, L33, PATU8902, KP3, PATU8988T, YAPC, KP2, PATU8988S, PK45H, PK59, HUPT3, HUPT4, SU8686, PANC0327, SNU213, SNU410, KCIMOH1, PANC0403, TCCPAN2, PANC1005, SNU324, PANC0203, PANC0213, PANC0504, and PANC0813. Pie chart represents percent of total hits.

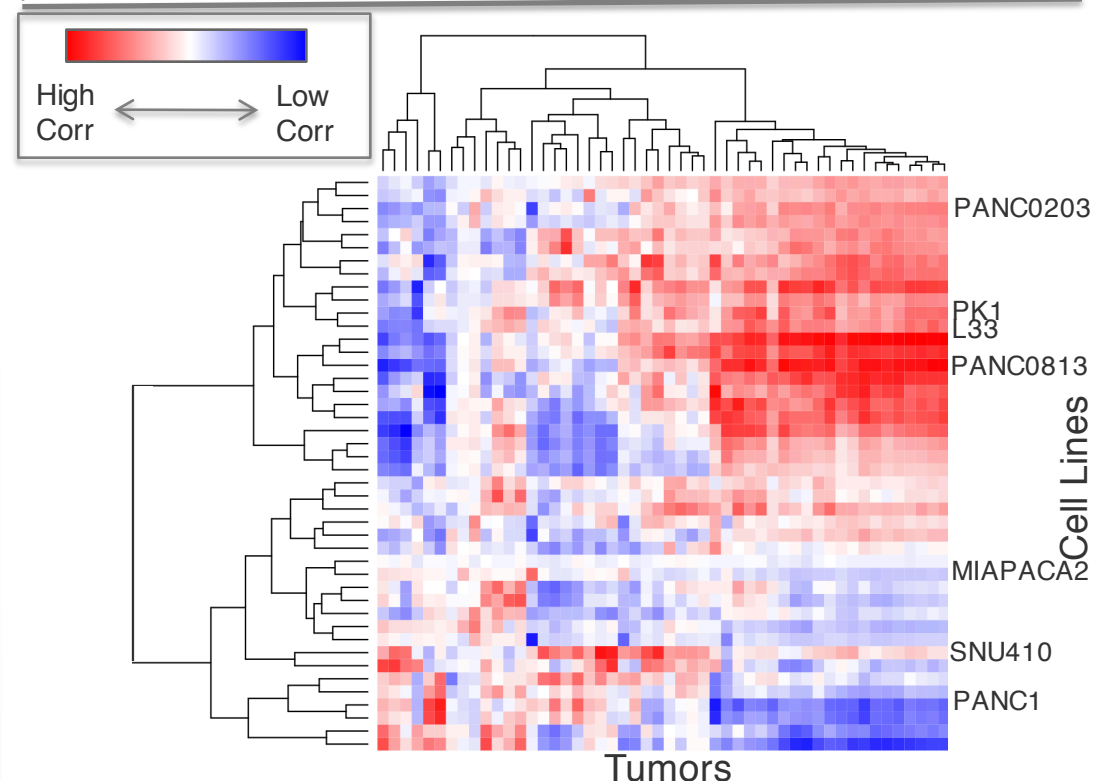


Figure 4. CNV correlation between cell lines and tumors. Correlation was calculated between each pancreatic cancer tumor and cell line. Some cell lines appear to have good correlation with many tumors whereas others do not. Overall, it was observed that cell lines have more CNVs than tumors, representing an important limitation of cell lines as models for tumors.

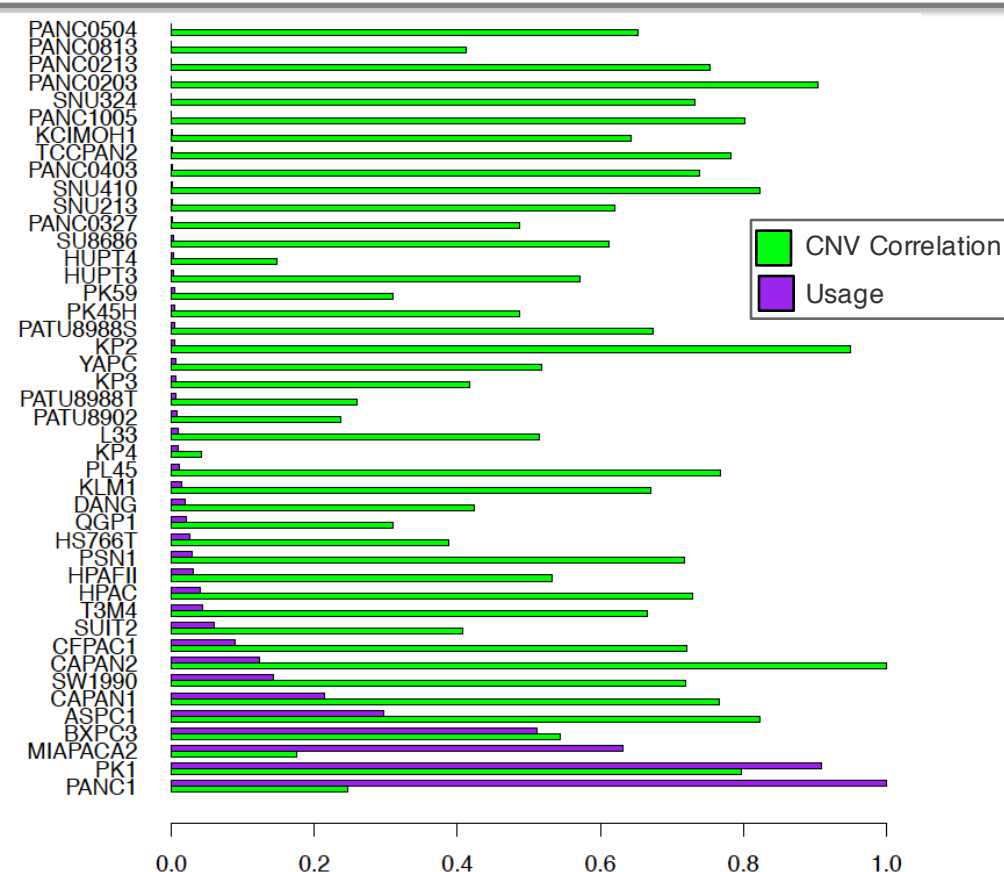


Figure 5. Comparing the median per gene CNV values in TCGA pancreatic cancer tumors and pancreatic cancer cell lines in CCLE. Alarming, the top five cell lines by CNV correlation with TCGA pancreatic tumors represented less than 10% out of all literature search hits for all pancreatic cancer cell lines, indicating that the most commonly used cell lines are not optimal from a genomics perspective. To bring CNV correlation and literature popularity to the same scale, both were divided by their respective max value.

Results (cont'd)

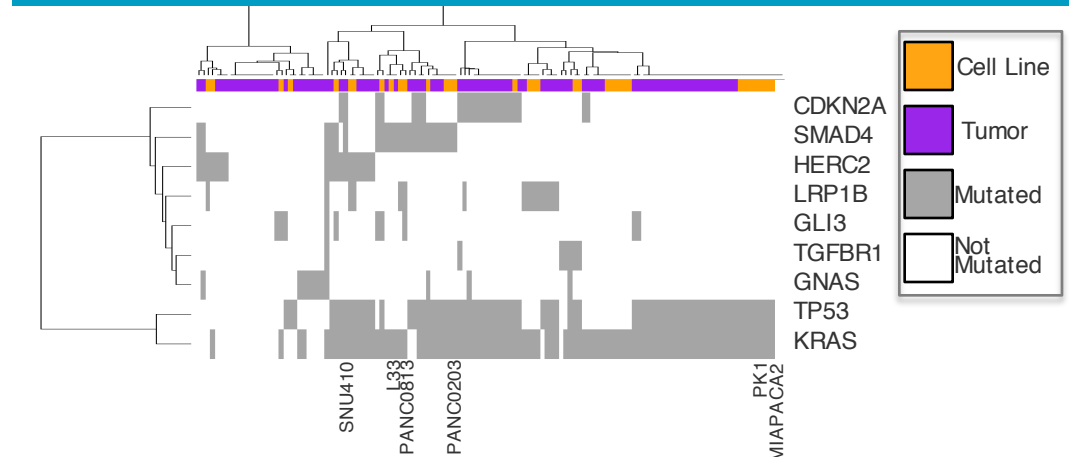


Figure 6. Using hierarchical clustering based on the presence or absence of the mutations passing filter, we showed that some cell lines readily clustered amongst tumors. Interestingly L33 and PANC0203 cluster in a branch with many tumor branches whereas MIAPACA2 occupies a branch tumors and cell lines that only have the TP53 and KRAS mutations.

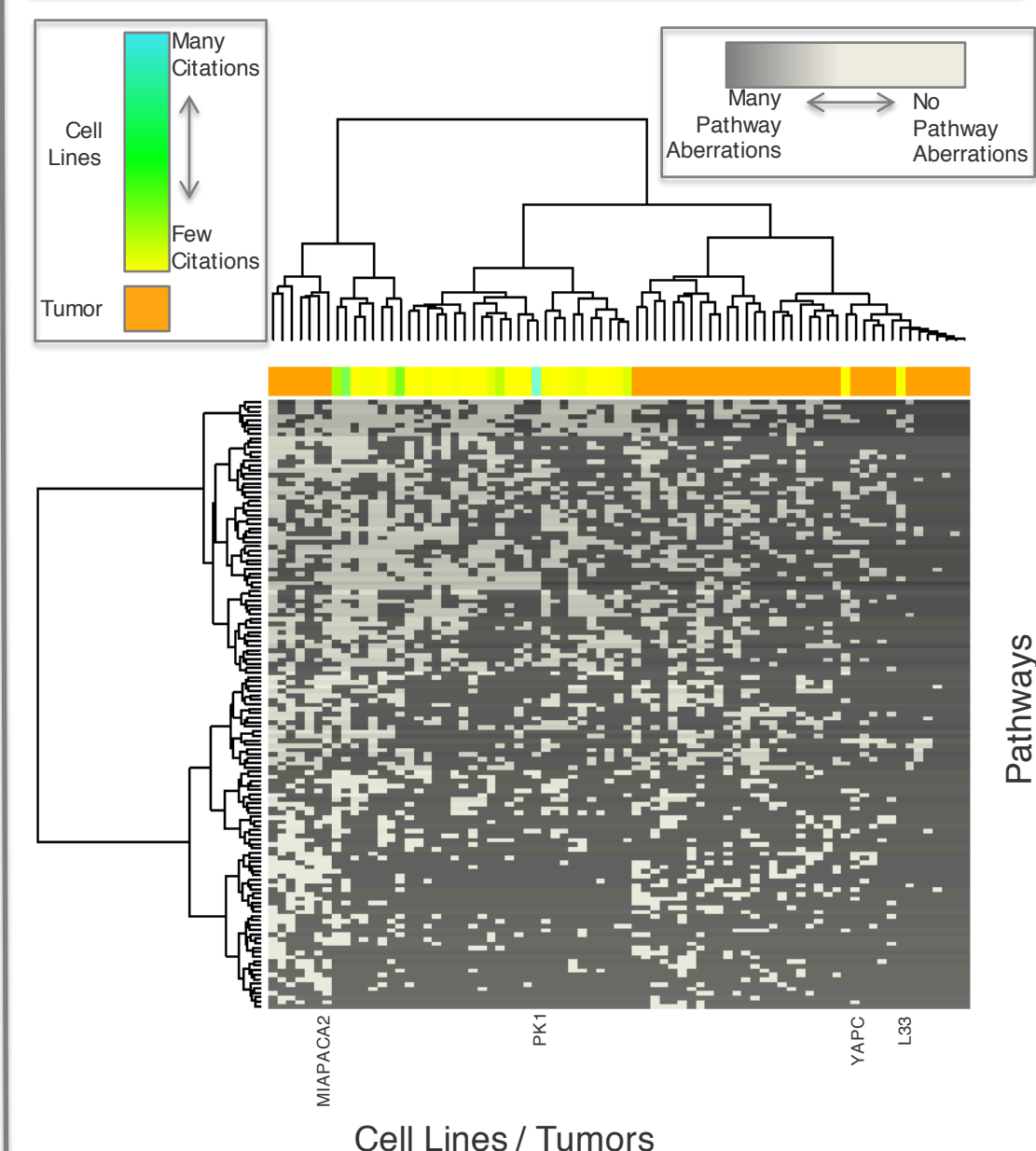


Figure 7. Select cell lines cluster with tumors. Interestingly L33 and YAPC cluster with pancreatic cancer tumors. All other cell lines cluster in branches composed of other cell lines. This shows that many popular cell lines may have genomic differences from tumors in important pathways.

Conclusions

- Based on the present analysis, some cell lines used less frequently in literature such as L33, SNU410 and PANC0203, may more accurately represent tumors as compared to popular cell lines MIAPACA2.
- Our work reports that many popular pancreatic cancer cell lines harbor distinct genomic aberration profiles from pancreatic cancer tumors and highlights the emerging role of genomics in advancing the clinical success of therapeutic trials by accelerate pre-clinical drug screening.

Future Directions

- It is possible to apply this method to other cancer types, given consideration for potentially different cancer biology.
- Drug response across patients is often heterogeneous, thus future methods will take genomic tumor subclass into account.