Genomics of Chemosensitivity

Den R.B. and Lehrer J. et al., 2017 "**Drug response variability between luminal and basal prostate cancer tumors" manuscript in preparation**

Disclaimer

This is a presentation of unpublished, proprietary data. It has not been peer reviewed or validated.

Motivation

- Patient chemotherapy response is variable and difficult to predict.
- The development of genome-wide tests such as Decipher have made full RNA expression data available for many thousands of patients.
- Prostate cancer management is evolving with emerging evidence supporting the earlier role of systemic therapy such as abiraterone and docetaxel (e.g., LATITUDE, STAMPEDE, RTOG 05-31/06-21, CST-553)
- There is a need for molecular signatures that can predict patient response to various chemotherapy options in localized prostate cancer.

Predicting Chemo Response

- Several cancer cell line panels with drug sensitivity data across many compounds are available:
  - NCI-60 (NCI)
  - CCLE / CTRP (Broad Institute)
  - GDSC (Wellcome Trust/Sanger/MGH)
- RNA expression data from cancer cell lines with drug sensitivity data allow us to mine for genes differentially expressed between responsive and non-responsive cancer cell lines
- RNA expression data from cancer patients on the Decipher GRID and tumor cell lines allows us to determine a patient's genomic similarity to responsive and non-responsive cell lines.
- We hypothesize that this genomic similarity, properly quantified, can predict patient chemotherapy response enabling better treatment selection and improved patient outcomes.

Calculating DRUG Response Scores (DRS)

- For any chemotherapy and patient, we compute:
  - A weighted average of
  - normalized expression of genes which are
  - correlated to cell-line sensitivity to the chemotherapy
- Or mathematically:

$$drugScore_{patient,drug} = \frac{\sum_{i \in correlatedGenes} coef_i * relativeExpression_i}{\sum_{i \in correlatedGenes} |coef_i|}$$

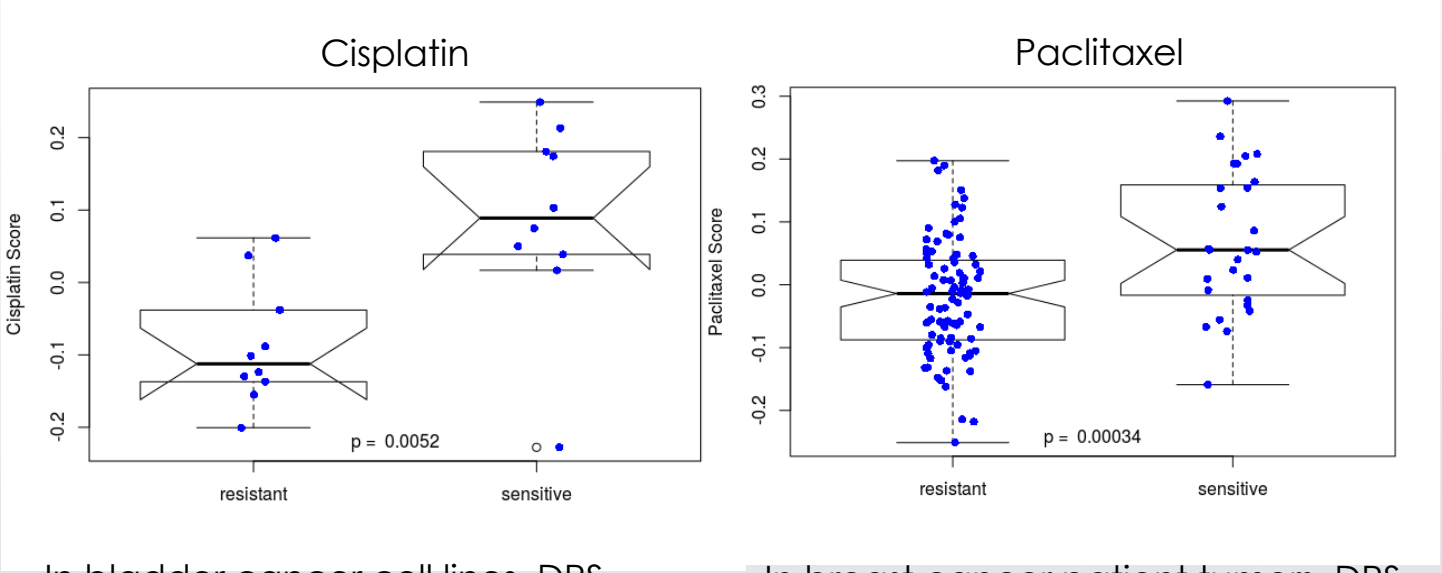
- In it simplest form, the coefficients can be taken from the gene's correlation to the chemosensitivity of the cell lines and multiplied by it's expression
- Higher scores indicate increased sensitivity for each drug/gene pair.

Methods

- 15,136 prospective RP patients basic clinical and pathologic data.
- 913 retrospective patients with treatment regimen, long-term follow up and outcomes
- 20 cancer cell lines with treatment regimen and response annotated
- Scores based on the NCI-60 and GDSC cancer cell line screens.
- Prospective patient chemo scores analyzed for correlation to 163 signatures and pathways from Decipher GRID.
- Prospective patient chemo scores hierarchically clustered using correlation distance and ward.D clustering method.
- Retrospective patient chemo drug response scores (DRS) evaluated as predictors of patient response to therapy.

Results

DRS significantly different in sensitive versus resistant cell lines and Patients



In bladder cancer cell lines, DRS Cisplatin discriminates between resistant and sensitive in vitro **(AUC = 0.86)**

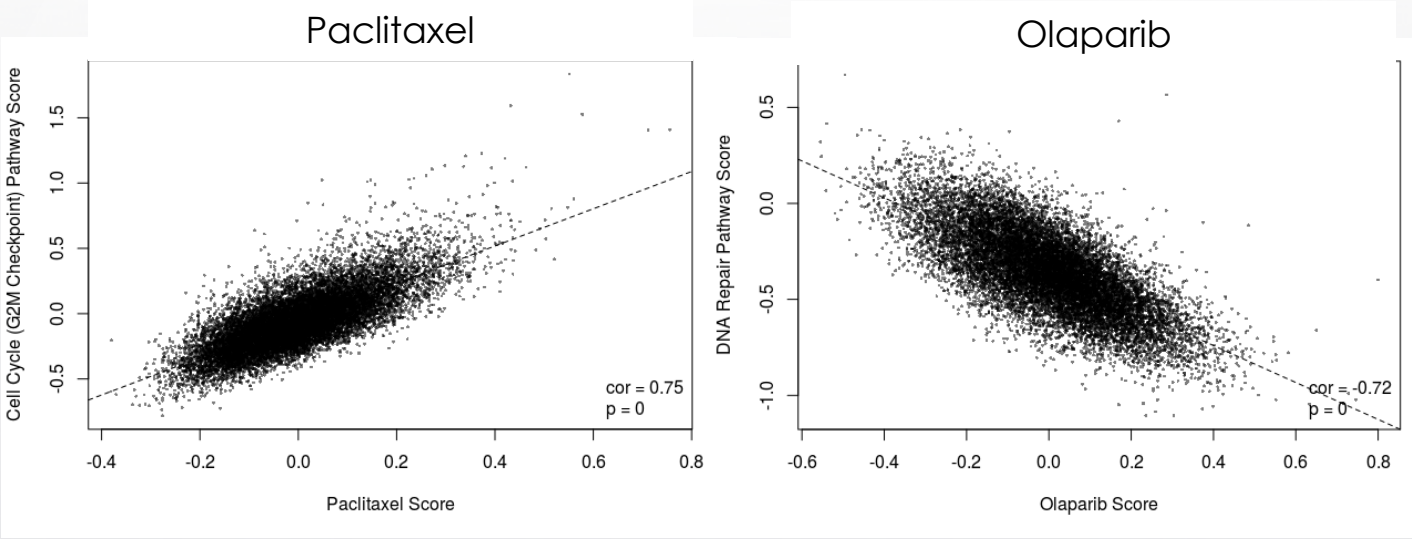
In breast cancer patient tumors, DRS Paclitaxel discriminates between resistant and sensitive in vivo **(AUC = 0.73)**

Validation in Treatment Response DatasetS

- In 10 publicly available treatment response datasets covering 913 patients and 20 cell lines, DRS scores are a significant predictor of chemo response in 5 datasets and trend towards significance in several others.

Sample Type	Treatment	N	DRS AUC (bold if significant)
Bladder cell lines	Cisplatin	20	**0.86**
Bladder cell lines	Paclitaxel	20	0.48
Breast patients	Docetaxel	24	0.66
Breast patients	Cisplatin	24	0.68
Breast patients	Paclitaxel	278	**0.58**
Breast patients	Paclitaxel	178	**0.66**
Breast patients	Paclitaxel	14	**0.80**
Breast patients	Paclitaxel	115	**0.73**
Breast patients	Paclitaxel	124	0.52
Breast patients	Paclitaxel	156	0.56

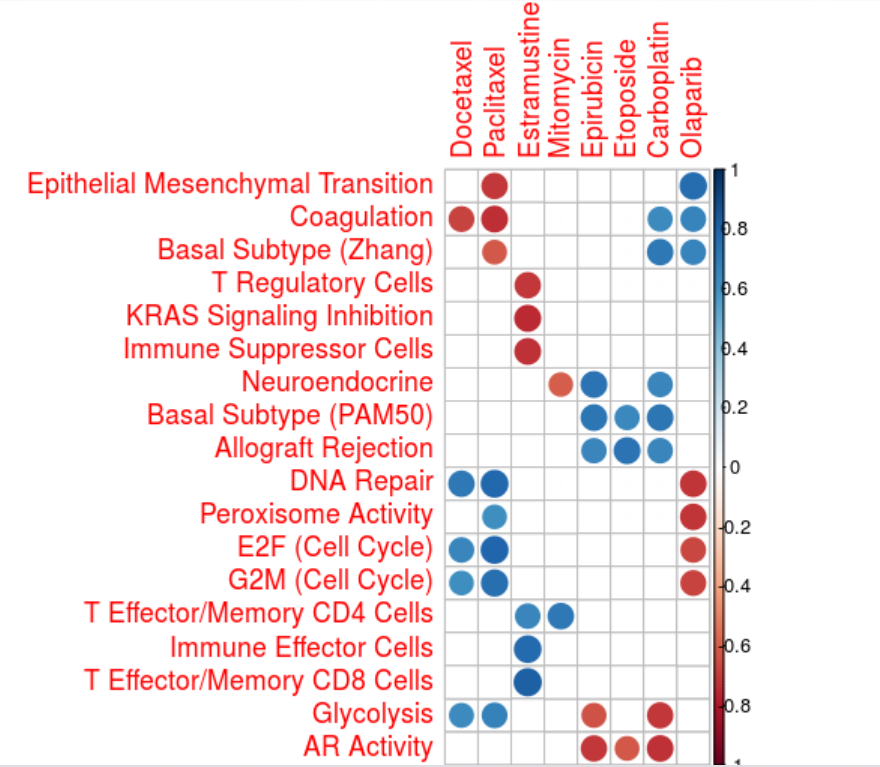
DRS correlated with tumor cell biology (PROlIFERATION and DNA-REPAIR)



Anti-microtuble drug response scores (DRS Paclitaxel) positively correlated with tumor cell proliferation.

PARP inhibitor drug response scores (DRS Olaparib) negatively correlated with DNA repair activity.

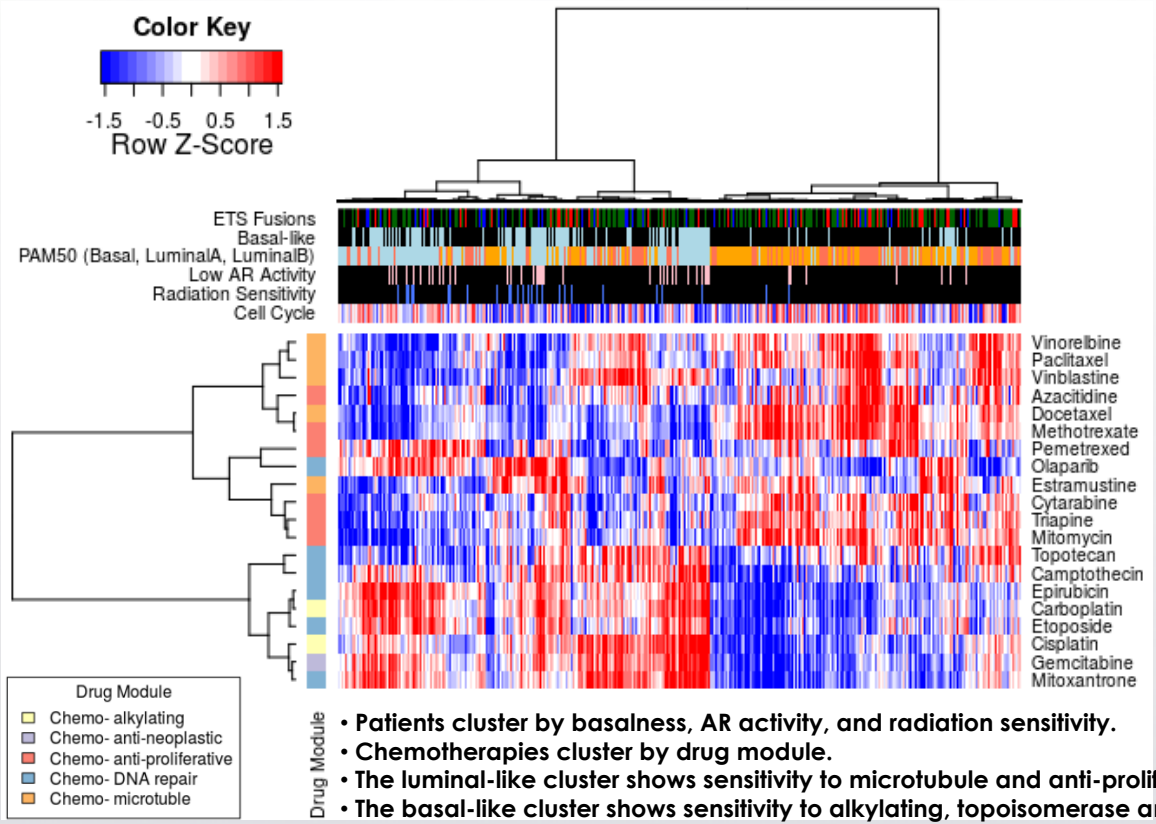
DRS scores highly correlated with cancer pathway signatures on GRID



- DRS for Taxanes positively correlated with cell cycle, proliferation, DNA repair
  - Neg. correlated with basal subtype
- Alkylating agents highly correlated with basal subtype, neuroendocrine
  - Neg. correlated with AR
- PAPR inhibitor highly correlated with basal subtype
  - Neg. correlated with DNA repair

Red circles- negative correlations
Blue circles- positive correlations

Heatmap of DRS in 15,136 RP patients



ERG+
ETS+
SPINK1+
Triple Negative

Basal-like
Luminal-like

PAM50 Basal
PAM50 LumA
PAM50 LumB

Lower AR Activity
Average AR Activity

Average RT Response
Higher RT Response

- **Patients cluster by basalness, AR activity, and radiation sensitivity.**
- **Chemotherapies cluster by drug module.**
- **The luminal-like cluster shows sensitivity to microtubule and anti-proliferative chemotherapies.**
- **The basal-like cluster shows sensitivity to alkylating, topoisomerase and DNA repair agents.**

Conclusions

- In a prospective dataset of 15,136 patients, DRS scores corresponded to expected biology and mechanisms of action
- Patients clustered into two groups on the basis of their predicted sensitivities.
  - These groups were distinguishable by characteristics such as molecular subtype and AR activity, and their sensitivity profiles were consistent with regard to class of chemotherapy.
  - Anti-microtuble directed agents (taxanes, vinca alkaloids) correlated to luminal subtype tumors, proliferation, AR activity and negatively correlated to EMT, immune infiltration
  - Anti-DNA directed agents (platinum, anthracyclines) correlated to basal subtype tumors and negatively correlated to DNA repair pathway expression.
- **Further validation is necessary**
- Nevertheless, this technology is a step in the right direction to improve patient treatment decisions with regard to chemotherapy.