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Predictive biomarker discovery method to bridge the gap between preclinical disease model dose-response and clinical trials

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Discovery of clinically relevant biomarkers in the preclinic

The translational gap between preclinical research and clinical development is a major cause of drug development failures. While high throughput omics methods facilitate the generation of large amounts of both in-vitro and clinical data, it is often the case where preclinical decision making is based on few models and no clinical data. To address this challenge, we sought to leverage the large existing clinical and preclinical data in order to derive predictive biomarkers before testing a drug in the clinic.

In this study, we present a machine learning based computational technique that integrates omics from preclinical studies and clinical treatment naive samples to create predictive biomarkers.

We evaluate the method on Cisplatin+PARPi and AKTi treatments in the context of breast cancer.

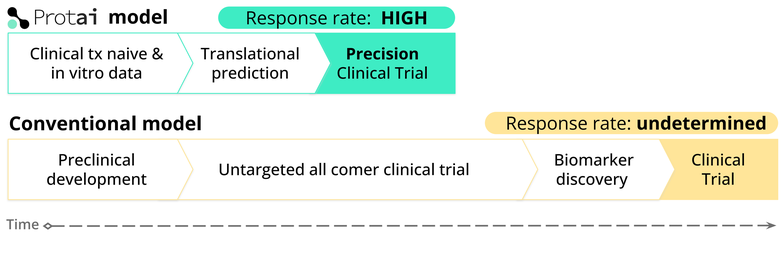

Figure 1. Conventional biomarker discovery workflow compared to Protai's model

Data: Harmonization of preclinical and clinical omics

For the derivation of the predictive biomarkers we utilize the Cancer Cell Line Encyclopedia (CCLE[3]) and Genomics of Drug Sensitivity in Cancer (GDSC[4]) as a resource for in-vitro dose response data for PARPi and AKTi, coupled with multi-omic molecular data. We also utilize the treatment naive molecular characterization from the Clinical Proteomic Tumor Analysis Consortium (CPTAC) data and TCGA of Breast cancer patients. These biomarkers are then evaluated on a test set obtained from the I-SPY2[5] adaptive clinical trial for HER2- patients treated with either Veliparib & Cisplatin or MK2206.

Clinical Tx naive dataset
n = 199 patients
- CPTAC[1] & TCGA[2] breast cancer
- mRNA, MS Proteomics
- Primary untreated surgically resected tumors without treatment or response data

Preclinical train set
n = 25 models
- CCLE[3]/GDSC[4] breast cancer
- mRNA, MS Proteomics, IC50
- Treated with Veliparib & Cisplatin / MK2206
- Both primary and metastasis

Test set
n = 131 patients
- 2 arms from I-SPY2 trial[5]
- mRNA, RPPA, pCR
- n=71: Veliparib & Cisplatin
- n=60: HER2- MK2206
- All samples are pre-treated

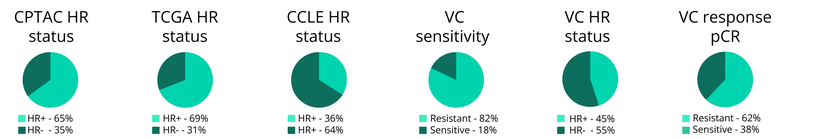

Figure 2. Overview of the data used for training and evaluation

Methods: Algorithm architecture

Separately for each treatment (PARPi and AKTi), we derived a clinically relevant protein subset (<20 proteins), calculated the model to patient similarity and trained a predictor on the weighted CCLE[3] & GDSC[4] data. Protai's biomarker discovery method is then tested on a validation data obtained from the I-SPY2[5] adaptive clinical trial with each PARPi and AKTi biomarker tested on the VC and MK2206 arms of the I-SPY2[5] clinical trial respectively.

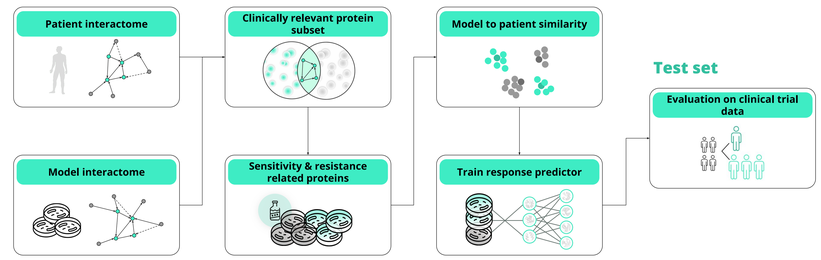

Figure 3. Algorithm and validation flowchart

Results: Protai's translational biomarker outperforms biomarkers derived from clinical data

We evaluate the Protai translational biomarker compared to results reported by the I-SPY2 investigators. Prospectively, HER2- patients were enrolled and randomized to one of eight treatment arms including the VC arm. *VC random HER2-* response rate is 38%, with 27 responders out of 71 VC treated patients.
Retrospectively, the investigators devised response-predicting-subtypes for optimal patient stratification for each arm. Optimal patient assignment for VC was based on *HER2-/Immune-/DNA-damage-deficiency(DRD)+* signature. The signature response rate is 60%, with 6 responders out of 10 signature selected patients.
The *VC Protai* translational biomarker response rate is 66%, with 19 responders out of 29 biomarker selected patients.

Similarly, the method was tested on HER2- patients from the MK2206 arm, where the I-SPY2 prospective response rate was 30% (18/60). Retrospectively, optimal MK2206 signature was HER2-/Immune-/DRD- signature, with 15% response rate (3/20).

An additional retrospective signature enriched for MK2206 response was HER2-/Immune+, with 39% response rate (14/36), nevertheless the optimal treatment assignment for this subtype was pembrolizumab, with 79% response rate (27/34).

Protai's MK2206 biomarker had 50% response rate (17/38).

Both Protai biomarkers were tested on the Ctrl arm (Paclitaxel) of I-SPY2 and were not associated with response to Paclitaxel, providing evidence of the biomarkers being predictive of response to the specific treatment (VC/ MK2206) rather then prognostic.

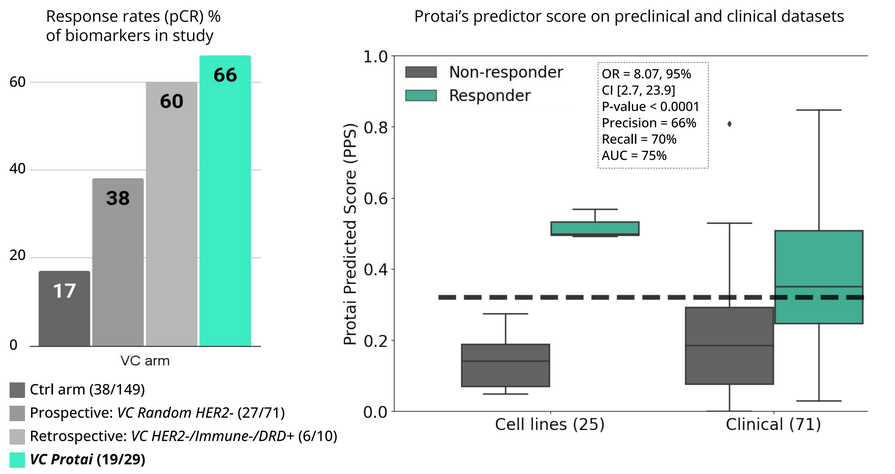

Figure 4. Left: Evaluation of the Protai translational biomarker (green) for VC compared to I-SPY2 biomarker results (shades of gray). Right: Box-plot depicting predictor score on cell lines and I-SPY2 test sets.

Conclusions and future research

- Protai presents a **novel computational biomarker discovery method** that uses pre-clinical dose-response and untreated clinical datasets.
- The method creates a **superior predictive translational biomarker much earlier in the drug development process**.
- The method suggests a novel efficient way to discover predictive biomarkers based on only in vitro data that **hold true throughout the drug discovery process.**
- Protai continues to improve the method as new test cases and data becomes more available.

References

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