Proteomics platform identifies vulnerabilities for DNA damage repair drugs

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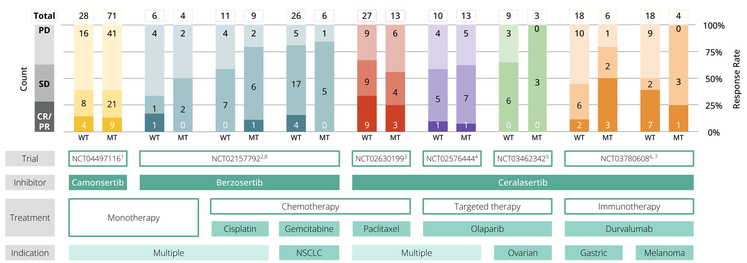
DNA damage repair drugs need better predictive biomarkers

- There are numerous drug development efforts of DNA damage repair (DDR) targets, such as PARP, ATR, ATM, CHK1 and others.
- Patients are routinely assigned to drugs based on BRCA mutation, or BRCAness profile, encompassing homologous recombination deficiencies (HRD) which don't always represent the responsive sub-populations.
- The ability to accurately identify responsive sub-populations for monotherapies and combinations is a major challenge.

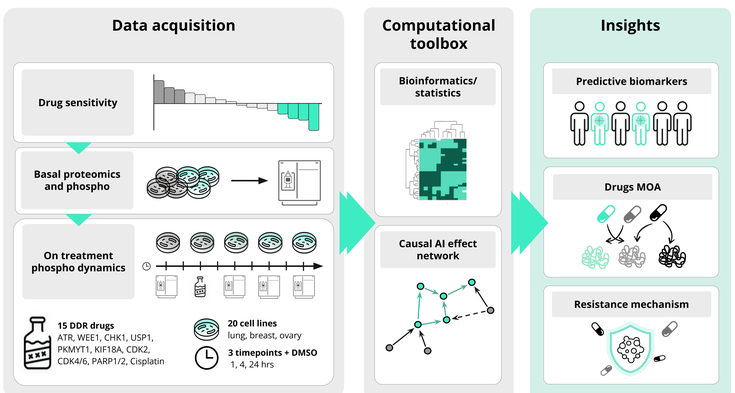
Meta-analysis of ATR clinical trials
Average response rate is 16.3%, independent of ATM/ BRCA mutation status
WT: 18.3% ORR*, Mutant: 13.9% ORR



Data and methods

The Protai platform leverages both public and private data consisting of: (1) Phenotypic drug sensitivity (2) Basal and dynamic phosphoproteomics.

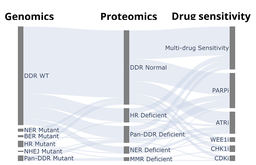
We apply computational toolbox including causal inference to answer precision medicine challenges such patient selection, drug MOA and resistance mechanism elucidation.



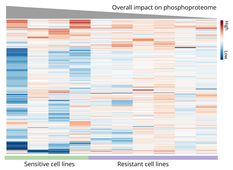
Proteomics and phospho dynamics reveal DNA damage signatures

- Comparison between genomic and proteomic DDR deficiency to DDR drug sensitivity (A).
- Using phospho-dynamic data, we observe multiple differences between sensitive and resistant cell lines (B, C, D) and between MOAs of DDR drugs (E, F) across different time points.

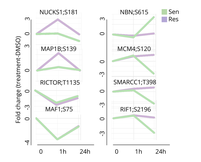
(A) ~40% of genomic DDR-wt lines exhibit proteomic DDR deficiency explaining DDR sensitivity



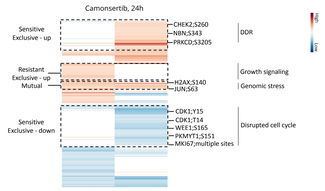
(B) Higher impact of ATR inhibition on sensitive cells



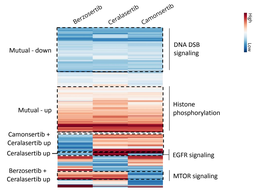
(C) Regulation is Time-dependent in ATRi sensitive and resistant lines



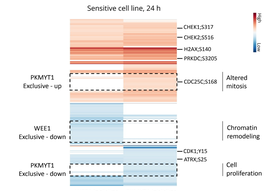
(D) Increased DNA damage and cell cycle disruption in ATRi sensitive cell lines



(E) Shared and distinct MOA of different ATRi treatments



(F) Shared and distinct MOA of WEE1 and PKMYT1 inhibitors



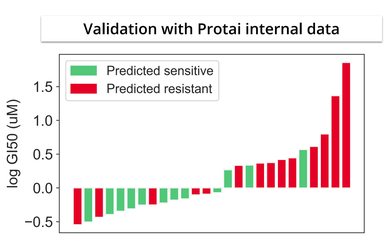
Discovery of a novel ATR biomarker

ATM-related proteomic signature predicts ATR response in cell lines

Leveraging the Protai precision medicine platform, we've trained a 10 proteins predictive biomarker (Protai Biomarker) on CCLE[9] and Ceralasertib data[10] and tested it on our internal data.

The Protai Biomarker exhibits improved precision and recall compared to the Genomic Biomarker, represented by commonly used mutations in the clinic.

Furthermore, the Protai Biomarker is not confounded by mutations.



Proteomic signature metrics surpassed genomic biomarker

	Precision	Recall	AUC*
Genomic Biomarker - ATM, ARID1A, BRCA1, BRCA2 loss of function mutations	0.62	0.36	0.55
Protai Biomarker validated on Protai internal data	0.75	0.64	0.78

* ORR = Overall response rate (CR and PR). ** AUC = Area under the curve

Causal AI learns unbiased effect network of DDR proteins

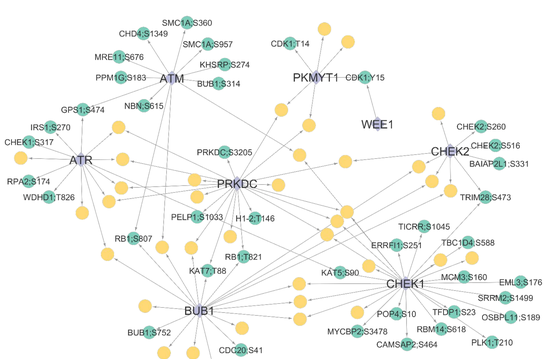
Learned network includes known and new kinase-substrate links

Leveraging our phospho-dynamic data and causal AI tools, we derive phospho-dependency network.

The underlying network contains causal links between phospho-proteins, enabling modeling the following virtual experiments:

1. What is the impact on the phospho-proteome of treatment with different drugs?
2. How does the phospho-proteins causal network vary in different cellular context?
3. What are the drivers of sensitivity and resistance?
4. What are possible combinations to overcome resistant?

The figure visualizes a subset of learned relationships, namely kinase-substrate relationships, demonstrating that both previously reported and new links were discovered.



Summary and future steps

- Protai's precision medicine platform elucidates:
  - Predictive biomarkers → improved response rates
  - Resistance mechanisms → combinations
  - Drug MOAs → competitive positioning
- The platform is consistently enriched by newly generated data
  - Additional PD data: inhibitors, time points, models and cell lines
  - Integration of molecular and phenotypic associations
  - Integration of clinical data and Protai's translational pipeline

Presented at the AACR-NCI-EORTC 2023 annual meeting

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